Comparative Physiology and Medicine Symposium –
to commemorate the work of Professor AR Michell

Wednesday 31 May 2017

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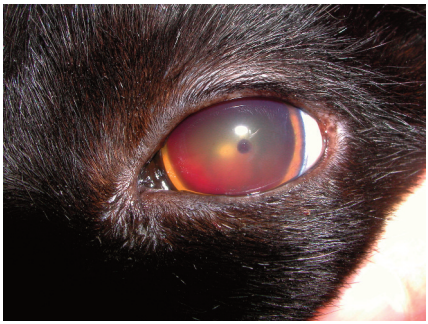
Welcome to the Royal Veterinary College

I wish you a warm welcome to this day of celebration and reflection upon the scientific career of a leader of our profession, Alastair Robert (Bob) Michell. Bob was passionate about science, driven by curiosity and a burning desire to understand both the similarities and differences between veterinary species and humans. Comparative medicine (now also referred to as One Health) was something he vigorously pursued as his academic discipline.

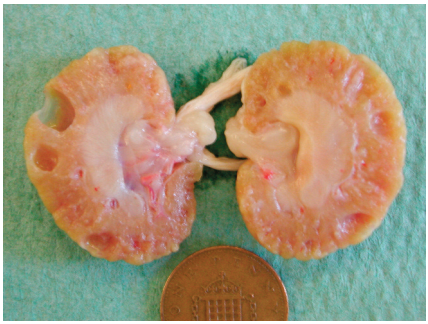
I hope he would have been pleased to see that this 'discipline' is alive and well at the institution he grew up in scientifically and within which he did so much to inspire the next generation of comparative medical scientists.

Jonathan Elliott

Professor Jonathan Elliott
Vice Principal for Research and Innovation



Hyphaema in a 15 year old male neutered domestic short-haired cat with severe hypertension



Small fibrotic kidneys from a 13 year old female neutered domestic short-haired cat which was euthanased due to severe chronic kidney disease

Royal Veterinary College
University of London

Programme

Great Hall

09.00 – 09.20 Registration and Coffee

09.25 – 09.30 Welcome from Professor Stuart Reid

09.30 – 09.50 Introduction (Professor Peter Lees)

Part I – Oral Rehydration Solutions (Chair – Dr David White)

09.50 – 10.20 Historical view of the concept of ORS and their development for use in calves (Dr Harriet Brooks, University of Bristol)

10.20 – 10.50 Diagnosis of acid base balance in diarrhoeic calves – implementation in practice (Dr Dai Grove-White, University of Liverpool)

11.00 – 11.40 Coffee Break and poster viewing

Part 2a: Assessment of kidney function and comparative nephrology (Chair – Prof David Church)

11.40 – 12.10 Measurement of GFR – a historical perspective to state of the art (Prof AM Peters, Brighton and Sussex Medical School)

12.10 – 12.40 Feline kidney disease – research at the RVC to achieve early diagnosis (Prof Harriet M Syme, Royal Veterinary College)

12.40 – 14.00 Lunch and poster viewing

Part2b: Assessment of kidney function and comparative nephrology (Chair – Dr Natalie Finch)

14.00 – 14.30 Measurement of GFR in the dog (Dr Allison Gleadhill, Crab Lane Vets, Harrogate)

14.30 – 15.00 Use of iohexol clearance in dogs as a diagnostic test – does it help in early diagnosis of kidney disease (Dr Ludovic Pelligand – Royal Veterinary College)

Part 3 – Hypertension (Chair – Prof Michael Herrtage)

15.00 – 15.30: Human hypertension and Genomics – current state of the art (Prof Mark Caulfield, QMUL)

15.30 – 16.00 Tea and poster viewing

16.00 – 16.30: Hypertension in the dog (Dr Angela Bodey, Abbey House Veterinary Hospital, N Yorks)

16.30 – 17.00 Hypertension in the cat – an overview of RVC research (Prof Jonathan Elliott, Royal Veterinary College)

17.00 – 17.20 Closing remarks (BVA/RCVS Presidents)

Memories of Bob by our speakers

Peter Lees, Royal Veterinary College

Personal reflections on Bob Michell: colleague and…much more

Bob Michell at RVC was, in succession, undergraduate student (on two degree programmes), postgraduate student, Lecturer, Reader and Professor. His degrees and postnomials were BSc (First Class Honours), BVetMed (with four prizes), MRCVS, PhD, DSc and FRSA.

Outside RVC, Bob Michell served his profession with distinction and dedication, being a member of RCVS Council (for 12 years), BVA Council (for 25 years), Association of Veterinary Teachers and Research Workers (AVTRW) and Veterinary Research Club (VRC). He advised many bodies, including The Royal Pharmaceutical Society of Great Britain. After leaving the RVC, he became Head of the Centre for Small Animal Studies of The Animal Health Trust.

Bob had significant leadership skills evident from an early stage of his career. He presided over RVC Students' Union Society, RCVS Council, AVTRW, VRC, the European Society for Veterinary Nephrology and Urology and RVC Alumnus Association; he served on the House of Lords Select Committee on Science and Technology and on the House of Commons Select Committee of Inquiry into Agricultural Research; he vice-captained RVC Student Boat Club; he chaired innumerable committees.

As a scientist Bob's disciplines were chemist, biochemist, physiologist (pre-emminently), pharmacologist, pathologist, clinician and statistician; seven in all, one for each day of the week. However, he was not chemist on Sunday and statistician on Saturday, but all disciplines on all days. This was the secret of his success. Within these fields his publications were in various forms; original research articles, textbook chapters, textbook (Sodium), reviews, in all numbering some 300. His skills as a communicator of science were extended to innumerable short reviews on a huge range of topics, most notably his famous and regular column in Veterinary Times. His contacts, associates and collaborators were numerous.

These are the bare facts. What they do not reveal are his impact on those he taught and those who worked with him and all who followed his publications, both academic and non-academic. His distinctive prose style added great weight to his writings. He successfully and repeatedly challenged current scientific thinking and thereby introduced new ideas and theories. Most significant of all, he built the bridges between the disciplines in which he excelled; this enabled others to cross the bridges in pursuing their own careers. In a nutshell, his greatest achievement was the application of pre-clinical data to clinical problems.

At an intellectual level, he provided solutions to many problems and at a practical level he provided solutions for conditions of fluid and electrolyte derangements. For me, it was for the design, through to clinical application, of these fluids ["you have problems, I have solutions"] that I shall best remember him. For others, we have the hypertension and renal disease stories and overall it was his pioneering of comparative medicine that colleagues will recall. He received many awards, including two of the BVA's most prestigious awards, the Chiron Award and the Dalrymple-Champneys Cup and Medal. These are testament to the contribution he made to both veterinary and human medical science, as a one health champion.

Bob needed to know the causes and consequences of everything; his curiosity was insatiable. At a personal level, he was a kindly, caring and charismatic person, but he wore his charisma lightly. He had a waspish sense of humour and was one of those rare individuals who could smile with his eyes. He never suffered fools gladly, but his put downs were gentle and civilised. His erudite criticisms of others' work were always courteous and well-informed. His comments and questions would invariably hit the bulls-eye, but were always put so as to generate support rather than cause offence. As stated in his Veterinary Record Obituary, Bob was a one-off; we mourn his passing whilst celebrating his life.

Dai Grove-White, University of Liverpool
Diagnosis of acid base balance in diarrhoeic calves – implementation in practice

I first met Bob in 1989 at a talk he presented to practitioners in North Wales on the subject of fluid therapy in calves. I had recently returned to Wales after a spell in the Middle East where I had attempted treating collapsed diarrhoeic animals with IV fluids (exact concentrations of table salt per litre estimated in terms of teaspoonfuls!). Results were variable but it whetted my appetite for the subject, so the opportunity to listen to someone on the topic was too good to miss. At the end of the meeting I went up to speak with Bob on my experiences and was met with total enthusiasm and encouragement. I left the meeting inspired and duly purchased his recently published Veterinary Fluid Therapy text and over the next few months devoured its contents becoming fascinated by "acidosis" such that I tentatively added sodium bicarbonate to my homemade solutions. In July 1990 at a BCVA meeting I was introduced to David White late one evening when the fluids were flowing. He told me about the Harleco and offered to loan one. This led to a collaboration with Bob and David which fired my enthusiasm for clinical research and eventually altered the path of my career. Prior to presenting the results of the first case series of calves at the BCVA, Bob read over the presentation and only one comment was made - "Music to my ears". For a simple farm animal vet, these were inspiring words. Inspiration was a talent that Bob possessed. Subsequently Bob encouraged me to carry out further studies and I was duly "the Bala outpost" of his RVC research group. My regular visits to the RVC and later to his house in Exning to discuss our findings were scientific and intellectual highlights of my time as a practitioner.

Bob's belief in the value of comparative medicine, arguably before it became the "One Health paradigm", was evident in his work on ORS and the convincing arguments he deployed regarding the divergence between veterinary and medical formulations, a subject he pursued with vigour and determination including challenging WHO on the subject. As well as the countless students and individuals such as myself he inspired, his role in the development of comparative medicine is a lasting monument to him.

Mike Peters, Brighton and Sussex Medical School
Measurement of GFR – a historical perspective to state of the art

I met Bob around 1990 when I worked at Hammersmith Hospital as a nuclear medicine physician. (Measurement of GFR in clinical practice is generally the responsibility of nuclear medicine departments.) Bob's interests in comparative medicine and renal function brought us together, along with Alison Gleadhill, Bob's PhD student at the time. We continued to collaborate when he moved to

the Animal Health Trust and I moved to Addenbrooke's hospital in Cambridge. Living closer together, we socialised more and I met his delightful wife, Pauline, and beloved dog, Merlin. In 1999, I was flattered to be invited by Bob to chair his invited open lecture at the Royal Society of Arts, *Only One Medicine*. One of Bob's passions was drug overdose in the elderly resulting from undiagnosed renal impairment, which is an almost inevitable consequence of growing old. Our final joint publication attempt – an article on this topic submitted to the British Medical Journal in 2012 – was rejected, much to Bob's annoyance! This was his response in an email to me: "…..what a silly, arrogant decision by BMJ".

Kidneys normally filter about 100 ml/min from plasma, which is 20% (filtration fraction) of renal plasma flow. This is the glomerular filtration rate (GFR). Urine flow rate is 1-5 ml/min. depending on climate and water intake, meaning that 95-99% of filtered water is reabsorbed in the renal tubule. GFR is measured using a filtration marker, which is a substance, not protein-bound in plasma, that undergoes filtration at the glomerulus and is neither reabsorbed nor secreted by the tubule. The distribution space of filtration markers is the extracellular fluid volume (ECFV). Inulin, the first marker used to measure GFR, is given by continuous infusion. GFR is calculated from urinary flow rate and plasma and urinary concentrations at steady state. It is then scaled for body size, usually surface area, though 3-dimensional whole body metrics make more sense. Nowadays, for convenience, GFR is measured clinically using radiolabelled filtration markers or iohexol given by bolus intravenous injection followed by a limited number of plasma samples up to 4 h post-injection to determine the plasma clearance, which for filtration markers is the same as urinary clearance and GFR. For further simplification, GFR can be measured from a single sample taken at 3-4 h. After mixing in the ECFV, filtration markers leave the ECFV exponentially with a rate constant that is close to the ratio GFR/ECFV and is therefore a convenient measure of GFR already scaled for body size. GFR is gender-dependent, declining with increasing age from about 40. Obesity distorts scaling but by itself influences GFR, differently between men and women. Renal reserve, which can be exposed in response to food and infusions of amino acids and dopamine, can be readily appreciated from the dramatic increase in GFR in the remaining kidney that follows donation. New imaging agents are available not only for measuring GFR but also for measuring individual kidney GFR, and imaging divided function between the kidneys and intra-renal distribution of GFR.

Harriet M. Syme, Royal Veterinary College

Feline kidney disease – research at the RVC to achieve early diagnosis

I first encountered Bob Michell when he tried to teach us renal physiology when I was a second year student at the RVC, more than 25 years ago. This is the point at which it would be nice to write that I was so inspired that I decided I wanted to become a veterinary nephrologist; sadly the truth was rather different, something I sometimes reflect on when our current students are not engaging with the material I am trying to present to them. Certainly, his lectures were quite entertaining; once we created a working model of the concentrating mechanism in the loop of Henle with decks of playing cards. However, the main thing I remember about his lectures was that we used to bet on how many minutes into the lecture it would be before he said the word "sodium" – it didn't seem to matter what the title of the lecture was, the smart money was always on a very early time point.

When I moved up to Hawkshead Bob (or Dr Michell as I expect we called him) became my personal tutor. He took great care of his tutees, meeting up with us frequently and diligently monitoring our progress. He would also invite us to his house for delicious dinners cooked by his wife Pauline. Several years after graduating I was giving one of my first external lectures at BSAVA and Bob and Pauline were both at the conference because he was president of something (RCVS?). Seeing that I was really nervous they undertook to come and sit in the audience as moral support – I remember Pauline said she was going to sit and knit as she knew nothing about veterinary medicine – I am quite sure they had better things to do with their time than to listen to me talk to the nurses about common poisonings, and I am not sure that their presence made me any less nervous, but I do remember being very impressed by their continuing pastoral care for an ex-tutee. So Bob's greatest influence on me was probably in moulding my view of what a good tutor does, and in my current role as senior tutor at the RVC this has consequences right across the college.

Allison Gleadhill, Crab Lane Vets, Harrogate
Measurement of GFR in the dog

After a house job at Bristol and some time in practice I saw a job advertised working with Bob Michell at London which appealed to me. Although I am primarily a clinician, as a veterinary surgeon my interest isn't purely clinical but very much the comparative physiology & comparative pathophysiology. There is a wealth of information out there both in the human medical field (where effectively man is the 'experimental animal' for veterinary species) and also in the zoological field (which I feel that the medics are pretty much unaware of).

The veterinary profession, as exemplified by Bobs career, has a broader perspective and capacity for lateral thinking which I hope we do not loose in an era of increasing specialisation amongst vets. This allows us to collaborate in projects that can benefit patients of all species and improve our understanding of disease and dysfunction we would have by having a narrow one-species perspective.

Bob was certainly keen on cross collaboration and this is a perspective we should be keen on maintaining.

Mark Caulfield, William Harvey Research Institute and Genomics England,
Queen Mary University of London
Human hypertension and Genomics – current state of the art

It was in the early nineties that I first came across Bob Michell at the London Hypertension Society where his insightful and challenging questions on aspects of renal physiology and blood pressure regulation brought an intellectual depth to the meetings. We agreed on the importance of hypertension which by 2025 will affect 1.5 billion people on the planet and will lead to half of the anticipated 17.5 million deaths worldwide from cardiovascular disease. Following from publications of the role of angiotensinogen in genetics of blood pressure Bob approached me regarding whether dramatic blood pressure differences between certain breeds of dogs could be used to highlight new physiology arising from genetic differences between dog breeds – a contrast that could not be done in humans. With his and Angela Bodey's enthusiasm we embarked on profiling the renin angiotensin

system in specific dog breeds. Bob then joined the William Harvey Research Institute at Queen Mary after his Presidency of the Royal College of Veterinary Surgeons and was a really valued and thoughtful contributor especially on renal physiology. Our last paper together was in 2011 written by Bob with Angela (they were very kind to include me - see below).

As a complex trait arising from genes and lifestyle, elucidation of the genomics of blood pressure needed national and now international collaboration and in the mid-nineties I established the MRC British Genetics of Hypertension Study which undertook family based genetic studies. This led to the Wellcome Trust Case Control Consortium which opened the era of genomewide association studies and finally in 2009 we began to identify new gene regions with modest influence on blood pressure. There are now almost 300 gene regions identified and these have highlighted new biology in both the kidney, the vasculature and elsewhere that may be harnessed for future treatment of high blood pressure.

Contents lists available at ScienceDirect

The Veterinary Journal

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Personal View

Evolution, essential hypertension and the high arterial pressures in certain athletic breeds of dogs

A.R. Michell *
A.R. Bodey
M. Caulfield
Harvey Institute,
St. Bartholomew's and the London Hospital,
Charterhouse Square,
London EC1M 6BQ,
UK
* *Address: Pinecroft, Upper Cleveley,*
Oxfordshire OX7 4DX, UK.
E-mail address: Bobmichell@hotmail.com (A.R. Michell)

Angela Bodey, Abbey House Veterinary Hospital, North Yorkshire
Hypertension in the dog

My first contact with Bob was when I applied for a post as clinical researcher at the Royal Veterinary College in early 1991. At the time, I was working in mixed veterinary practice in West Devon. I enjoyed my work, but felt as though my knowledge had reduced to that which I communicated daily to my clients, and I needed a new challenge.

The role that was advertised in The Veterinary Record concerned a clinical and comparative study of canine hypertension. My curiosity was aroused, though I confess I did not understand the job title!

When I met Bob, at interview for the post, he was warm and friendly, and set me at my ease, even though I felt completely out of my depth. He remained a warm and encouraging mentor throughout my time at the RVC.

Bob was always a man of questions. He could generate a probing question for every occasion, and was an inspiration in this regard.

Bob was an enthusiast for the huge resource to be found in clinical medicine. He recognised that careful collection of clinical data, with understanding of its reliability, was invaluable in generating an evidence base to inform ongoing developments in practice.

As I moved away from the university setting, returning to clinical practice, Bob's inspiration remained important in informing how I approached my clinical work, and the resource of clinical data. This was key in my ongoing involvement in aspects of breed health, especially recently amongst Irish wolfhounds, recognising the importance of this for the breed, to support understanding of breed difference, and inform comparative medicine.

Jonathan Elliott, Royal Veterinary College
Feline Hypertension reflections

I commenced my academic career at the RVC in 1990 – as a pharmacologist but with great interest in clinical physiology. It was fascinating to me to try to explain, from basic physiological principles, why clinical patients showed the clinical signs we noted. The pathophysiology of fluid and electrolyte disturbances interested me greatly and I had a wealth of clinical material from working in the emergency room as an intern at the University of Pennsylvania, that I could use in teaching. Bob gave me the opportunities to do this within courses he ran and inspired me, through wide-ranging discussions, to think of research questions that used the same approach.

Systems for measuring ionised calcium that could be used in the clinic became available soon after I started my lectureship and my attention was grabbed by a paper suggesting pregnancy-induced hypertension in women might be associated with low ionised calcium. As ionised hypocalcaemia reduced the ability of endothelial cells to produce nitric oxide – the newly discovered gaseous mediator that seemed to regulate blood vessel tone - this paper had a cellular mechanism to explain the clinical observation. With Bob's encouragement, I applied for my first grant from BSAVA Clinical Studies Trust fund and embarked on the study of ionised calcium in cats with chronic kidney disease. Twenty seven years later we are still working on feline CKD and hypertension and, although we didn't find a link between low ionised calcium and hypertension as I first hypothesised, I will always be grateful to Bob for his enthusiasm and his encouragement to explore the unexplained in clinical medicine.

Posters: on display in the Lightwell

	Title of poster	Researcher
1	Seasonal Variation in Blood Nitrite Concentration in Previously Laminitic and Non-Laminitic Ponies	Liz Finding
2	Evidence for updating feeding policies for pre-weaned dairy heifers in the calf	Claire Wathes
3	Investigation of synovial fluid on tendon injuries	Giulia Sivelli
4	Developing strategies to improve the healing of equine tendons using a surgical model	Ise Francois
5	• Cholesterol associated mitochondrial protein, TSPO provides protection from chemotherapy by facilitating retrograde signalling • Control of mitochondrial bioenergetics and structure by the ATPase inhibitory factor 1: a pro-survival relay via OPA1.	Radha Desai AND Danilo Faccenda
6	Muscle physiology/testing therapies for DMD	Dominic Wells/Ornella Cappellari
7	Modelling the rodent hindlimb.	Dominic Wells/Ornella Cappellari
8	Secondary osteons scale allometrically in mammalian limb bones	Alessandro Felder
9	Vascular calcification and bone formation: are they the same?	Jessal Patel
10	Establishing comparable conditions to study vascular calcification and bone mineralisation	Lucy Bourne
11	Mechanical manipulation of the tendon stem cell niche	Neil Marr
12	Interaction between inflammation and mechanical loading in endochondral ossification	Astrid Novicky
13	Effect of Piezo2 on osteoarthritis and the associated pain	Freija ter Heege
14	Controlling Cartilage to Bone Transitions for Improved Treatment of Bone Defects and Osteoarthritis: the role of in vivo modulation of mechanical signals	Soraia Silva
15	• Fracture-induced bone pain in a mouse model of femoral fracture • Immunohistochemical staining of a-klotho protein in feline kidney tissue	Ran Magnúsdóttir AND Henk van den Broek
16	The cat as a model of renal interstitial fibrosis: Characterisation of primary cultures of feline tubular epithelial cells.	Jack Lawson
17	• Fibroblast growth factor 23 and symmetric dimethylarginine in feline chronic kidney disease • B2 or not B2 mitral valve disease differentiating between stable and progressive cases	Hannah Sargent and Jenny Wilshaw
18	Breed, coat colour and hair length as risk factors for feline hyperthyroidism	Victoria Crossley
19	Comparative pharmacodynamics of oxytetracycline, tetracycline and doxycycline in calf respiratory pathogens: Matrix and drug effect	Andrew Mead
20	Dynamic pharmacometrics: Hollow-fibre infection PK PD modelling of veterinary antimicrobials	Andrew Mead