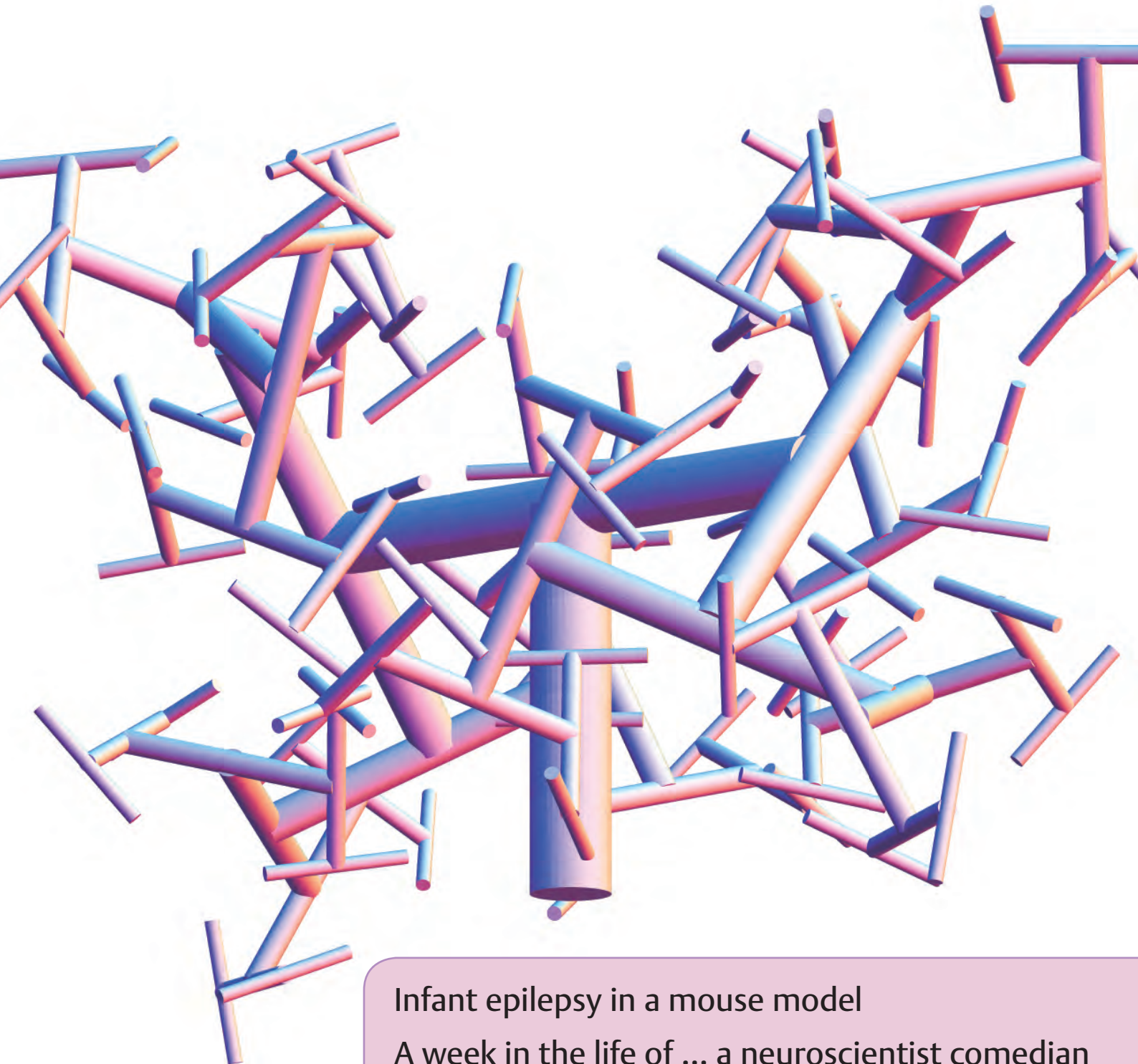


# PHYSIOLOGY NEWS

winter 2009 | number 77



Infant epilepsy in a mouse model

A week in the life of ... a neuroscientist comedian

How words and rituals change brain circuitry



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The Society's dog. 'Rudolf Magnus gave me to Charles Sherrington, who gave me to Henry Dale, who gave me to The Physiological Society in October 1942'

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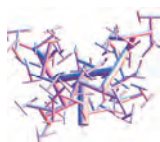
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Advancing the science of life



Cover image: an 'H-fractal'. From Tan & Taylor, pp. 25

# PHYSIOLOGY NEWS

## Action points

### Grants

The Society offers funding through the following grant schemes: Travel Grants, Non-Society Symposia Grants, Outreach Grants, International Teaching and Research Grants and the Vacation Studentship and Departmental Seminar Schemes. For full information, please visit: [www.physoc.org/grants](http://www.physoc.org/grants)

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## Physiology News

### Deadlines

Letters and articles and all other contributions for inclusion in the Spring 2010 issue, No. 78, should reach the Publications Office ([magazine@physoc.org](mailto:magazine@physoc.org)) by **14 January 2010**. Short news items and letters are encouraged, and can usually be included as late copy if space permits.

### Suggestions for articles

Suggestions for future articles are welcome. Please contact either the Editorial Administrator or a member of the Editorial Board of *Physiology News* (see contents page for details).

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These guidelines are intended to assist authors in writing their contributions and to reduce the subsequent editing process. The Editorial Board of *Physiology News* tries to ensure that all articles are written in a journalistic style so that they will have an immediate interest value for a wide readership and will be readable and comprehensible to non-experts. Scientific articles should give a good overview of a field rather than focus entirely on the authors' own research.

### Format of articles

The main message or question posed should be introduced in the first paragraph. The background for the topic should then be established, leading up to the final conclusion.

### Length of articles

This will be determined by the subject matter and agreed with the Senior Production Editor.

### Submission of articles

Authors should submit articles as a Word document attached to an email. Illustrations should be sent as separate attachments (see below) and not embedded in the text.

### Illustrations and authors' photographs

Authors are encouraged to submit diagrams, drawings, photographs or other artwork with their articles and a photograph of the author(s) should accompany submissions. Illustrations and photographs may be colour or black and white, and preferably TIFF, JPEG, PNG, PDF or AI files with a **minimum resolution of 300 dpi**.

### References

Authors are requested to keep the number of references to a minimum – preferably no more than two or three. Please cite all references in the style of *The Journal of Physiology* (see *Information and Guidance for Authors* at <http://jp.physoc.org>).

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## In this issue

Welcome to the final *Physiology News* of 2009.

This stage of the year usually brings a round-up of the summer's conferences, and this year is no exception – I think I counted nine reports – or it might have been ten or eleven! – including reports from three continents.

An unusual 'Week in the Life' this issue gives us – the neuroscientist-comedian. Neuroscientist-writers are perhaps not all that rare, but comedians are rather scarcer. Though, as writer Dean Burnett points out, there are ex-scientist, or ex-doctor, comedians – such as the Irish Dara O'Briain (BSc Maths & Theoretical Physics, UC Dublin) or British comic Harry Hill (MBBS St Georges Hospital Medical School). Trying to juggle the comedy and the science is even more of a challenge, as Dean describes in his diary (p. 14).

Scientific content is served with six News and Views articles, as well as the latest in what is already proving to be a very popular *Techniques* series. Something a bit unusual can be found on p. 30, where Fabrizio Benedetti *et al.* discuss the physiology, and brain circuitry, of the placebo response. Placebo therapies also get a look-over in a somewhat different context on p. 40.

This issue we are saying hello to a slate of new journal Editors, new Society Council Members, and new office staff, all of whom tell us something about themselves (pp. 45 and 51).

Finally, as well as saying hello, the issue also features some goodbyes. Goodbyes can be celebrations of the careers of colleagues who are reaching well-deserved retirements (pp. 7 and 10) – though of course they may not really be retiring. Some goodbyes, like obituaries, mark sadder occasions (pp. 54 and 55). Even then, though, we can and should celebrate the life, and career, of scientists and friends.

## Targeted spending – is it good value?

The Department for Business, Innovation and Skills (BIS) was created on 6th June of this year, expanding the politically re-born Peter Mandelson's empire considerably, by the merger of the short-lived Department for Innovation, Universities and Skills (DIUS) and the Department for Business, Enterprise and Regulatory Reform (BERR). Lord Mandelson heads a mega-department of six ministers including fellow peer, Paul Drayson, the new Minister for Science and Innovation. Lord Drayson's background is as a technologist; he graduated in Production Engineering from Aston University, from where he later obtained a PhD in Robotics. A wealthy businessman – he describes himself as a 'high-tech entrepreneur' – his recent speeches suggest that his agenda for science is strongly influenced by his background in enterprise.

Basic scientists tend to be wary of importing organisational solutions from the world of profit-driven business. So are we to expect more of the same? Will new initiatives push us further towards the situation in which the hapless 'Cressida Cormorant' found herself in last issue's *Unbelievable!* article?

Lord Drayson's perception of British scientific success stories, as reflected in his reported speeches, certainly focuses on technological excellence: the World Wide Web, MRI scanners, satellites, earth observation, space and materials science [1]. Of course, this could reflect an agenda of trying to make science spending palatable to the wider public, in an era of austerity, by focussing on things that are more familiar to people. However, these are also the examples he tends to name-check when talking to specifically scientific audiences. Where he speaks of success in the biological sciences, examples have included the recent British contribution to the pan-European collaboration that witnessed an oesophageal replacement using a patient's own stem cells and our capacity for undertaking large scale clinical trials [2]. He is so captivated by trials of stem cell therapies that he has mentioned them in at least three speeches. Again, this may be part of a dual agenda, where it is mainly the wider public being addressed. A more worrying interpretation would be that it reflects the limit of Drayson's understanding of research in the biosciences.

There is a saying: 'He who pays the piper calls the tune'. Academic research

scientists are paid, for the most part, by public funds, and hence it is reasonable that the public should know what it is getting for its money. The good news is that Lord Drayson has reiterated that the science budget is safe – funding earmarked for science cannot be redirected to meet shortfalls created by the economic downturn. He has also stated his belief in the 'Haldane principle', that the distribution of science funding should be determined by scientists. The worry, though, is the nature of the tune. What of basic science? Of physiology? Lord Drayson says that he understands the serendipity of science, and that without basic science, opportunities for its application are non-existent. The Office for Life Sciences Blueprint has even acknowledged a skills gap in *in vivo* sciences, including physiology, and established an industry and HE forum that – by the time this article is published – will have agreed actions to address the gap [3]. And yet in another breath, Drayson wants 'a healthy and ongoing situation where scientific insight translates into profitable business' [1]. When critics of this approach have labelled it as flawed, as it reduces the likelihood of unexpected discoveries, he stated bluntly, 'I think they're wrong'.

To take an alternative view, some scientists may feel Lord Drayson is entitled to think as he pleases, as long as he is prepared to consider that central tenet of scientific endeavour, evidence – or rather, lack of it. There is little evidence that identifying specific areas to which science funding should be targeted increases productivity or innovation. The government's Foresight programme is an excellent example of an organisation designed to identify such targets. It has been going since 1994, which gives us a good decade's worth of outcome, allowing 5 years of leeway to get projects off the ground. Foresight's aim is 'to increase UK exploitation of science' and, according to its web page blurb, to 'identify potential opportunities for the economy or society from new science and technologies, and actions to help realise those opportunities'. It even has a 'horizon scanning centre' where you can perform a 'sigma scan'. Before you get too excited, this is just a set of 271 summary papers compiled from more than 2000 documents, and interviews with 300 leading thinkers, that explore 'potential future issues and trends over the next 50 years which may have an impact on UK public policy'. We arguably already have a superior version of this – it is called the scientific literature. Incidentally, typing 'physiology' into

sigma scan reveals that according to Foresight we're not about to make an impact.

So what, in the first 5 years of its life, did Foresight recommend be funded? Research into: integrative biology, neurodegenerative diseases, ageing, genetic disease risk factors, new classes of therapeutics, recombinant technology, diagnostic applications of molecular biology, and immune manipulation. All, no doubt, logical enough bits of crystal ball gazing. So what, according to them, has this focus actually achieved? Somewhat surprisingly, the Foresight website fails to comment on the above areas but states that they have supported Green Technology (most laudable) and inspired the Royal Society of Chemistry, the Institute of Biology and the Institute of Physics to collaborate on a series of workshops on future sources of energy.

The single thing prioritised by Foresight that has actually made rapid commercial strides is (largely non-biological) nanotechnology. Foresight in the '90s did not identify Lord Drayson's favourites, stem cells, as 'hot', even though they were discovered in the '60s. Even if they had, a recent worry is that induced pluripotent stem cells are disturbingly similar to cancer cells – suggesting stem cell therapies are far from imminent [4]. Meanwhile, vast sums have been spent on genome-wide association studies, although only a modest proportion of risk for common heritable disease is explained by common genetic variants [5]. These examples rather bear out the publicly expressed misgivings of scientists (e.g. [6]) as to the advisability of large-scale targeted research.

So, it appears that predicting where money should be best spent is trickier than it seems. One wonders if there will ever be a study to test the view, common among scientists, that a combination of curiosity and 'chance favouring the prepared mind' – serendipity, if you prefer – will do the job just as well.

### Patricia de Winter

1. 'How can science help build a better future?' Speech by Lord Drayson at the Cheltenham Science Festival, 3rd June 2009.
2. 'UK life sciences: ensuring a healthy future'. Academy of Medical Sciences Forum Annual Lecture delivered by Lord Drayson at the Royal Society, 3rd March 2009.
3. Life Sciences Blueprint. Statement from the Office for Life Sciences. July 2009. [http://www.dius.gov.uk/innovation/business\\_support/ols](http://www.dius.gov.uk/innovation/business_support/ols)
4. Krizhanovsky V & Lowe SW (2009). *Nature* **460**, 1085–1086.
5. Frazer KA *et al.* (2009). *Nat Rev Genet* **10**, 241–251.
6. Alberts B (2008). *Science* **319**, 1733.



## The hypothalamic paraventricular nucleus in health and disease

A symposium 'Bristol II' was held on Sunday 12th July, 2009 at Baker's Hall, Brasserie Blanc, The Friary Building, Cabot Circus, Bristol, organized by David Murphy, Mike Ludwig and Julian Paton.



The venue for Bristol II meeting: Baker's Hall, The Friary Buildings, Cabot Circus, Bristol. In 1227 this was originally built as a Religious House founded by Maurice de Berkeley for the Dominican Order (Black Friars).

There were over 100 attendees to this highly successful meeting. David Murphy informed us that the venue of the meeting was of great historical importance as it was built originally in the 13th Century as a place of worship for Dominican Friars. After Henry VIII dissolved the monasteries in 1536, Baker's Hall became a private dwelling. Then, in 1670, it was converted into a Quaker meeting house. It was here that, in 1696, William Penn (founder of Pennsylvania) was wedded at the age of 52 to a 24 year old local lass called Hannah Callowhill. It was also remarked that, coincidentally, one of the organizers (Julian Paton) was wedded in the building in 1996, some 300 years after Penn. So what of the excellent science that was communicated during the day:

It is clear that the paraventricular nucleus (PVN) is a major integrating structure that both receives a plethora of afferent inputs and regulates numerous systems simultaneously. In this symposium, we considered the role of the PVN in the control of food intake, blood pressure, blood volume, plasma

osmolarity, dehydration, stress, pregnancy, temperature, and learning and memory. Based on our discussions it became clear that the PVN is a master of ceremonies and orchestrates neuronal, hormonal and autonomic function to maintain bodily homeostasis. In addition, the PVN appears to be a culprit in numerous disease states in terms of its role in the excessive sympathetic nerve activity that is generated in obesity, hypertension, heart failure and diabetes (metabolic syndrome).

In addition to conventional neuronal synaptic inputs to the PVN, this structure also receives information from forebrain circumventricular organs, via chemical messengers released from the blood-brain barrier or resulting from circulating chemicals or white blood cells that trigger release of mediators from either the endothelium and/or glia that encase them. Certainly, under certain conditions of pathology, glia become activated and communicate with PVN neurones. It is proposed therefore that the

blood-brain barrier surrounding the PVN is not a barrier *per se*, rather a filter that allows signalling from blood-borne chemicals and cells. From our discussions, it is clear that these non-conventional lines of communication affecting PVN neurone excitability (e.g. vascular-neuronal; vascular-glia-neuronal) require further interrogation. It may also be influenced from higher brain centres including the cerebrum, leaving open the question as to whether it is also a command nucleus regulating the set point of numerous bodily functions.

Based on many papers presented, it was evident that there is a major role of the immune system in controlling PVN activity. While this was described to play a role in the homeostatic control of vasopressin release, there was abundant evidence that cytokines and chemokines affect PVN activity under conditions of hyperosmolarity, high levels of angiotensin II, heart failure and hypertension. Future studies clearly need to identify



Participants enjoying the sunshine and luncheon interval at Bristol II. Top: Colin Sumners and Mohan Raizada (both University of Florida) with one of the organisers (David Murphy, University of Bristol). Below: old friends unite! Scott Young (left; NIH) and Stafford Lightman (University of Bristol).



Delegates at Bristol II meeting came from far and wide. These three young physiologists are from Serbia, Germany and Poland.

the source or sources of these mediators (adherent white blood cells, endothelium, neurones and/or glia) as this remains unknown but will be essential knowledge in guiding potential new therapeutic interventions.

Clearly, with the complexity of this nucleus in terms of controlling multiple functions, it becomes important that interventions are both spatially controlled and cell specific. Most presentations included attempts to target different cell types within the PVN. Magnocellular *versus* parvocellular neurones can be pinpointed based on their spatial separation within the nucleus but a note of caution is needed in the intrinsic inter-cellular signalling that occurs between these cell groups through dendritic release of vasopressin. Nevertheless, attempts are being made to genetically manipulate vasopressinergic *versus* oxytocinergic *versus* glutamatergic *versus* glia cells within the PVN as well as interneurones *versus* output neurones such as those with projections to the rostral ventrolateral medulla or spinal cord. This is being made possible by the use of transgenesis (germline and somatic). This ever increasing sophistication of approach is clearly working and significant rapid advance in our understanding of the PVN is being made.

Questions remain as to how unique the changes in the PVN are between different disease states such as heart failure, obesity and hypertension. There was some evidence that signalling mechanisms and

alterations in gene expression show a high degree of overlap between diseases; this requires clarification. Additionally, we need to determine how representative the mechanisms are in the PVN to other brain regions controlling the same function in health and disease states. This was clearly out of the scope of the present meeting, designed to focus on PVN specifically, but could form the basis of a future meeting.

The presentations had a rich integrative flavour of using multiple techniques and measuring multiple physiological responses. This significantly contributed to their quality as well as the information gleaned. However, despite this, it became evident that to further our understanding of the PVN in integrating physiological outcomes in health and disease, more effort in the future is needed to combine studies across laboratories with specific interests; for example, stress response during pregnancy and alterations in blood pressure control with an emphasis on pre-eclampsia. Also laboratories monitoring food intake and obesity should join forces with those measuring blood pressure and sympathetic activity to look at common PVN mechanisms. An emphasis on chronic studies is essential for onward translation into man and the clinical environment. It is hoped that an outcome from the present meeting would be the initiation of discussions on such collaborative efforts.

The meeting resulted in a number of high-profile collaborations, many of



Some speakers at Bristol II enjoying the symposium dinner. From left to right: Song Yao (University of Bristol), Mike Ludwig (University of Edinburgh), Javier Stern (Medical College of Georgia) and William Rostene (UPMC, Paris).

which are already moving forward in terms of collaborative experiments, laboratory exchange visits, joint grants and future meetings.

The following represents feedback from speakers and attendees at the meeting:

*"I'd like to thank you once again for inviting me to speak at the PVN meeting. I had a fun and educational time. I'm sure everyone else did. Everything was great."* W. Scott Young (NIH)

*"I would like to thank you again for your hospitality during the PVN meeting. It was a very nice program and in a nice location. It was a beautiful day."* Bayram Yilmaz (Turkey)

*"I had a great time in Bristol! The meeting was certainly interesting and jam-packed."* Jaideep Bains (Calgary)

*"I would like to thank you for giving me an opportunity of joining the meeting in Bristol. It has been very useful scientifically and that's very kind of you also for your hospitality."* Haluk Kelestimur (Turkey)

*"It was a great meeting you organized in Bristol. Relax full of science and great talks and atmosphere. It seems that it is a great place to work your both labs in Bristol."* William Rostene (Paris)

*"I just wanted to let you know that I had a great time in Bristol, and I thank you for giving me the opportunity to participate in the meeting. I think it was a great and successful meeting! I'm looking forward already for the next one!"* Javier Stern (Augusta)

*"The venue was outstanding and the sessions excellent. You really know how to put on a great show."* Willis Samson (St Louis)

We would like to thank the following for supporting the meeting:

British Society for Neuroendocrinology  
The Physiological Society  
The University of Bristol (Faculties of Medical & Veterinary Sciences and Medicine & Dentistry)  
The University of Florida  
The Wellcome Trust

**Julian Paton**



## Epithelial form, function and environment

Epithelia and Membrane Transport Themed Meeting, Newcastle (6–8 September 2009)

On the 6th September 2009 Newcastle University Epithelial Research Group welcomed Members, Affiliates and guests of The Physiological Society to the first Epithelia and Membrane Transport Themed Meeting. The line-up of invited speakers, without exception leading experts in hot and emerging topics of epithelial research, promised a broadly focused, exciting and vastly informative conference. The meeting attracted 152 registered participants, the majority from the UK. However, scientists travelled from as far as New Zealand, Australia, India, Ukraine and Chile to attend the meeting. The scientific programme included 16 invited talks, 25 oral communications and 37 poster presentations. The Themed Meeting was organised by Mike Gray and Andreas Werner of the Institute for Cell and Molecular Biosciences, Newcastle University.

The meeting got off to an impressive start with Sir Nicholas Wright's (Cancer Research UK, London) insights into intestinal stem cells and their contribution to tumourigenesis. Further presentations focused on transdifferentiation (David Tosh, University of Bath) and epithelial morphogenesis as well as the cellular structures involved in these processes (Diane Barber, University of California, San Francisco, USA; Markus Affolter, University of Basel, Switzerland and John Sayer, Newcastle University). The highlight of the second day was without doubt the talk on aquaporins given by Nobel Laureate Peter Agre (Johns Hopkins Malaria Research Institute, Baltimore, USA). The variety of aspects covered in the session was impressive: cutting edge molecular investigations into the cellular physiology of epithelial transporters as well as translational studies were presented (Edith Brot-Laroche, INSERM, Paris, France; Dianne Ford, Newcastle University; Stefan Broer, Australian National University, Canberra, Australia and Jashvant Unadkat, University of Washington, Seattle, USA). Gavin



Peter Agre with local organizer Mike Gray.

Stewart (University College Dublin, Republic of Ireland) concluded the day with the Biller Prize Lecture, which focused on the physiological roles of urea transporters: from bacteria to ruminants and man. The third and final day of the meeting focused on various molecular structures and networks that allow epithelia to adapt to a changing environment in different organs (Jim Anderson, University of North Carolina, Chapel Hill, USA; Tomas Ganz, University of California, Los Angeles, USA and Marshall Montrose, University of Cincinnati, USA). Particular emphasis was given to the regulation of ion and fluid balance in epithelia with keynote presentations from Ole Petersen (University of Liverpool) and Richard Boucher (University of North Carolina, Chapel Hill, USA).

Days 1 and 2 were concluded with dedicated poster sessions that saw eminent experts, students and postdocs engaged in scientific discussions over a glass of wine or a beer. The Physiological Society's Blue Riband Poster Competition was won by Havovi Chichger (University College London) followed by Alice England (University of Sheffield) and Tetyana



Alejandra Heredia and Mariano Otero.

Chorna (Ivan Franko National University of L'viv, Ukraine).

A special highlight of the Meeting was The Society Dinner held at *As You Like It* restaurant in Jesmond, Newcastle. The evening entertainment included smooth jazz music from Sarah Morton and Jesse Reed and a fantastic tango performance from Alejandra Heredia and Mariano Otero, who mesmerised the distinguished audience with a breathtaking show.

The feedback from the meeting was overwhelmingly positive; networking and the interaction with young scientists was highlighted; however, the quality and the breadth of the science were particularly recognised. We would like to thank all who contributed to the success of the Meeting, with special thanks to Sarah Barnsley and Nick Boross-Toby (The Physiological Society). We gratefully acknowledge the industrial sponsors and The Physiological Society for financial support.

At the end of the conference a meeting was held to discuss future Epithelia and Membrane Transport themed events, mainly focussing on the next themed meeting in 2011. Symposia were also discussed and although theme members have been very successful at securing symposia at the main 2010 meeting, it was agreed that a strategy is required to preserve this strong presence, including appointing someone to act as an initial point of contact for coordinating symposia bids and disseminating information. Stuart Wilson (Dundee) and Doug Bovell (Glasgow) announced that they are organising an Epithelial Physiology meeting next year in Dundee, on 2 and 3 September, which would be open to all Physiological Society Members. It is hoped that this may become a biannual event. We would like to thank everyone who stayed on for this meeting and contributed to the very positive discussions.

All in all the conference vividly demonstrated that epithelial physiology is alive and kicking, and hopefully has paved the way for many more successful events.

**Andi Werner and Mike Gray**



## Festschrift symposium in honour of Edward J Johns

Hormonal, molecular and  
neural control of the kidney



Left to right: Jonathan Emmerson, Jacek Manitius, John Coote, Edward Johns and Gerard DiBona.

In August 2009, Edward Johns retired as Head of Department of Physiology, University College Cork, Ireland, following a highly active, productive and continuing career in the field of renal physiology. Prior to taking up this position in January 2002, Edward spent the majority of his academic life at the University of Birmingham, but also formed strong links with a worldwide network of collaborators, trainees and friends during this time. Edward's career has spanned over four decades to date and has included major research, academic and scholarly outputs. Furthermore, aspects of his work have produced direct impacts on the clinical management of hypertension in patients suffering from chronic renal failure. Edward has been a Member of The Physiological Society since 1985 and was elected Convenor of the Renal Physiology Special Interest Group between 1998 and 2000. He has been a powerful force for collaboration within his field, having trained researchers from, and having made sabbatical trips to, numerous countries during his career. Edward is regarded with the greatest warmth, esteem and respect by everyone with whom he has interacted: this was reflected by the atmosphere of a festschrift symposium held at the Brookfield Health Sciences Complex, University College Cork, on the 17–18 September, in honour of his career.

This event included presentations by speakers hailing from six different nations and four different continents, indicating the global scale of

Edward's influence on this field. I had the pleasure of introducing this symposium and could not resist reference to a sentence from the book *Ulysses* by the Irish writer James Joyce, likely to strike a chord with renal physiologists 'Most of all he liked grilled mutton kidneys which gave to his palate a fine tang of faintly scented urine.' The first speaker was Jacek Manitius (Medical University of Bydgoszcz, Poland), who gave a moving account of Edward's supervision of his postgraduate research in renal physiology. This was followed by a presentation by Michael Snow (University College Cork, Ireland) on atrial receptors and renal function, which sparked some intense debate about the relative contributions of peripheral and central neural inputs to renal function. Next, Kenju Miki (Nara Women's University, Japan) gave a fascinating seminar on the benefits of immersion in hot springs and the physiological effects that this has on the vascular and renal systems. John Coote (University of Birmingham, UK) ended the first session with a talk on the roles of central and peripheral peptides determining cardiac–renal responses.



Left to right: Akio Nakamura, Margaret Johns, Edward Johns and Gerard DiBona.

Following lunch, Gerard DiBona (University of Iowa, USA) discussed neural influences on kidney function in the context of Edward's life, including his love of sailing and of making tea in 'the correct way'. Ulla Kopp (University of Iowa, USA) extended this theme with a talk on the role of afferent renal nerves in renal regulation of sodium homeostasis. Both Gerard and Ulla have had long-standing interactions with Edward at both personal and professional levels. Indeed, Gerard acted as Edward's best man at his wedding to Margaret.

That evening, a dinner celebration was held in the Kingsley Hotel, Cork which included speeches honouring Edward Johns. The dinner went very well and was a social occasion attended by many of Edward's friends and colleagues. Of particular note were Olga Hudlicka, an esteemed colleague from the University of Birmingham, and Jonathan Emerson, Edward's third PhD student to graduate (out of a total of 30 to date), having a reunion with his PhD supervisor for the first time in 24 years.

The first speaker on the second day of this symposium was Akio Nakamura (University School of Medicine, Tokyo, Japan), who described the use of viral vector delivery of  $\beta$ -2 adrenergic receptors for treatment of kidney disease. The final speaker was Ged Davis (University of Otago, New Zealand), on the topic of baroreflex control of the kidney in a rat model of obesity, a particularly pertinent topic given the increasing prevalence of this disorder and its associated pathologies in the Western world. The meeting was brought to a close by some video presentations by individuals who were unable to attend in person. The highlight of these was a slideshow by Raj Handa (Indiana University School of Medicine, USA), which magnificently summed up the consensus, glowingly positive viewpoint of Edward as both a scientist and a human being. In my own Southeast London vernacular, Edward truly is 'a scholar and a gent'.

I would like to take this opportunity to thank Patrick Harrison and Gordon Reid, who helped organise this event. We are extremely grateful to Margaret Johns, our co-conspirator in this venture, and to all of the speakers and attendees whose efforts and generosity made this such a wonderful occasion. Finally, we are highly indebted to The Physiological Society for generously providing a Special Symposium grant, which, in combination with funding from The Society for Endocrinology, made this fantastic event possible.

**John Mackrill**

## Lighthouses and lobsters in Woods Hole

When I first saw the call for papers for the Muscle in Health and Diseases meeting organised jointly between the Society of General Physiologists (SGP) and The Physiological Society, I was determined to attend.

Organised by David Eisner and H. Lee Sweeney, the meeting offered an impressive list of speakers and a range of research from the basic to more clinical. It also presented the opportunity to visit a place I fell in love with over 10 years ago. Thus, at the beginning of September I found myself in Boston wondering if the trip would live up to expectations.

Woods Hole is situated in Massachusetts, Cape Cod and is the gateway to Nantucket and Martha's Vineyard where some of America's rich and famous spend their holidays. The village of Woods Hole and surrounding area also contains several research institutes, including the Marine Biological Laboratory (MBL), and has a vibrant scientific community. The MBL has research laboratories on site and offers numerous excellent courses including one on zebrafish development and genetics, which I attended 10 years ago. As anyone who has stayed at the MBL will know, the rooms are minimal and most of your time is spent on science. As soon as I had dropped off my bags I found myself engrossed in the first evening symposium focused on myosin and molecular motors, which included some eye-catching movies on motor function. True to form the morning session, the contractile apparatus, started bright and early at 8.30 am with talks on mechano sensing and the supermolecule titin, plus electrical and metabolic remodelling in cardiac tissue. After a break for coffee, to help combat that early start, the talks shifted towards disease, starting with hypertrophic cardiomyopathy and then membrane dysfunction associated with muscular dystrophy. The first full day was brought to a



View of the Eel pond at Woods Hole from Swope Centre.

close with a presentation on the potential therapeutic targets to treat the myofibril mutations that cause cardiomyopathy.

Friday began with work on ryanodine receptor diseases and research that explores the detailed structure of the calcium release units. My short talk on the regulation of myofibril organisation in developing skeletal muscle was in this session and I was honoured, if a little intimidated, to find myself sharing a stage with very eminent scientists. The calcium



Lobster supper on the last evening in Swope Dining Room.

signalling theme continued with a presentation on L-type calcium channels, and the ryanodine receptor coupling and calcium balance in cardiac fibres. In the afternoon, despite the weather and much debate regarding a possible gale, the scheduled boat trip around the harbour did go ahead. Perhaps fortunately no great whites were spotted, as had been reported at the seal colony up the coast, but we did see some of the beautiful coastal scenery that has made this area famous. For those that hadn't

brought their sea-legs there was also the walk up to the Nobska Lighthouse. Later, after recovering from the afternoon activities, the session on disease and repair was started with several presentations on Duchene muscular dystrophy and was wrapped up with uterine smooth muscle activity. There was still just time to squeeze in discussions in the mixer sessions and, if you still had the stamina, at the Captain Kid pub.

The final day of the conference started bright and early again with a continuation along the theme of disease and repair, this time with a focus on smooth muscle. There were also presentations on the spatial control of pH in heart function and the development of cell replacement therapies. Kevin Campbell gave the Keynote address on the dystroglycan complex and the mutations that generate muscle disease. The meeting wound down with a lobster supper, poster award presentations, after-dinner drinks and a trip to Captain Kid for those that didn't have to get up too early. The location was as I remembered and had a relaxed atmosphere, the sessions were full of interesting science, centred on physiology, and provided an opportunity for plenty of discussion. So back in London and with time to reflect, I ask myself did the meeting live up to expectations and I have to say I 'would wholly' recommend it to anyone!

**Rachel Ashworth**  
Queen Mary University of London



## Translating 'omics' into functional and clinical applications

Thelma Lovick enjoyed the buzz at the 7th James Black Conference

In the 1990s, with the molecular biology revolution in full swing, rumblings started about the dearth of expertise in the classical techniques that had underpinned research in physiology and pharmacology for decades. Molecular biology was sexy. It was fast and gave clean answers to well-defined questions. Genetic modification was exciting. The possibilities offered by knockouts, knock-ins and other 'omics' wizardry seemed endless. High throughput became a buzzword (it still is) and classical *in vivo* physiologists, those with blood under their fingernails (the health and safety police hadn't really got on to this yet) were left standing alongside their slow, sometimes messy preparations and long experiments, bowed by the weight of more and more draconian Home Office regulations. They were labelled as dinosaurs and we all know what happened to them.

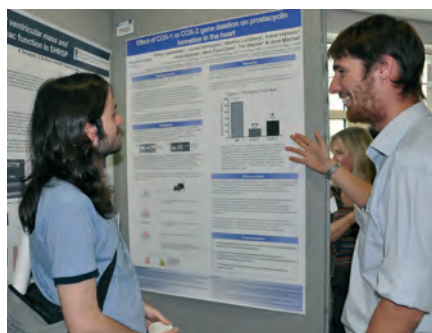
But this didn't happen to physiology.

Within a few years the new word on the street was 'translational'. How were the fabulous advances of molecular biology going to get out of the PCR machine and into real life? Only with the help of integrative physiologists and pharmacologists. Except that by now they were pretty thin on the ground. It became not uncommon to advertise for a postdoc to work on an *in vivo* project and to receive no applications from suitably qualified British candidates. The Physiological Society and the British Pharmacological Society decided to survey the *in vivo* training opportunities offered in UK universities and discovered that less than 2% of undergraduates studying physiology or pharmacology received any *in vivo* experience (1). But the survey was even more worrying – 25% of the academic staff

who could teach these essential skills would be retiring in the next 5 years and there were no replacements! Big Pharma could also see that the UK was going to lose its competitive edge in research and development, and a consensus report: *In vivo sciences in the UK: sustaining the supply of skills in the 21st century*, published by the Association of the British Pharmaceutical Industry and the Biosciences Federation reached similar conclusions (2). It contained a very clear recommendation: more training in *in vivo* skills at all levels and fast. In 2007 £12million was made available from a unique consortium of funders: BBSRC, the BPS, MRC, KTN, HEFCE and SFC and a call went out for bids for Capacity Building Awards in Integrative Mammalian Biology which were designed to rebuild *in vivo* training capacity. Four Centres for Integrative Mammalian Biology have now been established at King's College London, Imperial College London, and consortia from Manchester and Liverpool Universities and the Universities of Glasgow and Strathclyde.



Mike Collis presents a prize for best poster to Craig Robertson (Glasgow).



Philip Leadbeater (Imperial College) discusses his poster with David Farmer (Glasgow).

This year the 7th James Black Conference, a joint venture by The Physiological Society and the British Pharmacological Society, was held at King's College London on 1–3 September. It was organised and led by Mike Collis (our CEO) who co-ordinates the Integrative Mammalian Biology initiative and has been closely involved from the start. The meeting, *Integrative Pharmacology and Physiology – translating 'omics' into functional and clinical applications*, provided a showcase for the exciting developments that are taking place in the field of integrative mammalian biology. Over 3 days, formal presentations were delivered mainly by staff members of the abovementioned Centres, interspersed with some excellent short talks by their postgrads and postdocs. Topics revolved around four themes:

Pain, inflammation and injury

Models of cardiovascular disease – from bench to bedside

*In vivo* approaches to studying metabolism

Models of immuno-inflammation and infection: clinical predictive validity

The speakers highlighted the use of new technology for *in vivo* research and the integration of molecular technology into the *in vivo* approach. There were exposés on a wide range of topics including the use of adenoviruses to optimise the outcome of vein grafting *in vivo* (Andy Baker), how 2-photon microscopy *in vivo* can be used to image the development of atherosclerotic plaques (Pasquale Maffia), the use of luciferases for cell and disease tracking (Nurea Andreu), and metabolic profiling and inbreeding to generate models of disease (Chris Stevenson). A cautionary tale from Ian Machin (Pfizer) warned about the risk of generating false positive data if behavioural studies are not adequately blinded and Catherine Lawrence (Manchester)

told us how chronic systemic inflammation in obese mice leads to breakdown of the blood–brain barrier and influences stroke outcome. The programme ended with a presentation by Kathryn Chapman (National Centre for the Replacement, Refinement, and Reduction of Animals in Research), which focussed on the funding opportunities for research into the refinement (good welfare equals good science) of animal research and the use of the most appropriate species (e.g. rodents rather than primates for addiction studies).



Mhairi Macrae (Glasgow, centre) with Ross Brett and Bob Jones (Strathclyde) at the dinner. Photographs by Ivor Williams.

Mindful of the needs of the predominantly young audience, an early evening session at the end of the first day was devoted to career development and funding opportunities for early career scientists. Throughout the meeting, more than 70 posters were displayed, reflecting the diverse range of *in vivo* research topics

that is currently being pursued at institutions throughout the UK. There was also a section on the all-important teaching of *in vivo* sciences in undergraduate courses.

This meeting was extremely successful and very well organised. Participants were able to spill out from the single lecture theatre into a poster viewing area where lunch, tea and coffee were served and plenty of time was allowed for going round the posters and for the essential networking. The meeting was topped off by an excellent dinner at the nearby Waterloo Brasserie, and diners were required only to stagger the 200 metres back to their accommodation, conveniently situated across the road from the conference venue, ready for the next morning's early start. The mood of the meeting was resolutely upbeat. The overall funding situation may still be pretty dire but it is clear that investment in *in vivo* research in the UK is paying dividends. This is a very encouraging sign. Rather than the oft repeated refrain of 'too little too late', maybe this time it will be 'just enough and just in time'. I do hope so.

### Thelma Lovick

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1. Leggett M (2005). Teaching of *in vivo* research techniques in UK universities – wide-ranging and prompt action is needed. *Physiology News* 60, 39–40.
2. [www.abpi.org.uk/publications/pdfs/invivo\\_brochure.pdf](http://www.abpi.org.uk/publications/pdfs/invivo_brochure.pdf)

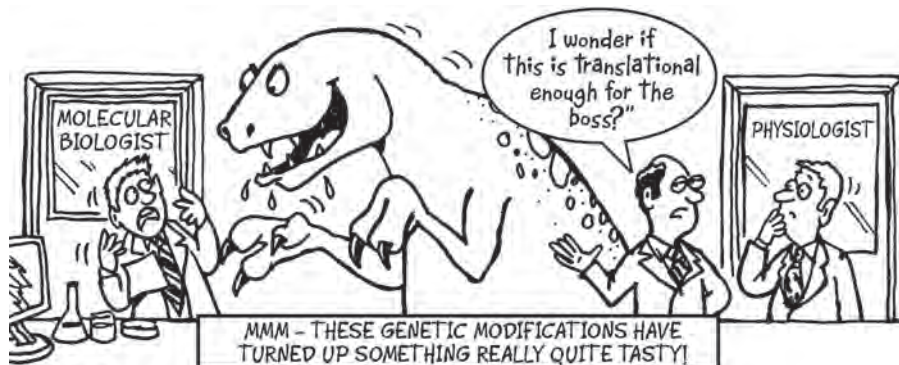
## Festschrift in honour of John Russell



The Centre for Integrative Physiology, University of Edinburgh, organised a very special event to honour and celebrate the life and achievements of John Russell (pictured above). The festschrift was held on Wednesday July 1st, 2009 and almost 100 people gathered at the Hugh Robson Building to hear talks from many of John's friends and colleagues, past and present.

John started in his career in science over 30 years ago, publishing more than 150 papers. Over the years he has held several offices: most notably he was the head of the former Department of Physiology at the University of Edinburgh and President of the International Neuroendocrine Federation. He is the current Editor-in-chief of the journal *Stress*. John has been chairman, organiser or co-organiser of many meetings, including the World Congress on Neurohypophysial Hormones and the World Congress on Stress, and he is again active in organising the next 'Parental Brain' meeting here in Edinburgh in 2010.

As first or second supervisor he trained over 25 PhD students, and the list of former and present postdoctoral fellows, national





and international visitors and collaborators who have worked with John is endless.

I was glad to see that so many of them followed my call to come to Edinburgh. The program included talks from Hiroshi Yamashita, Takashi Higuchi, Mike Kawata, Tatsushi Onaka (Japan), Colin Brown (New Zealand), Richard Ivell, George Fink (Australia), Tony Plant, (USA), Quentin Pittman (Canada), Rainer Landgraf, Inga Neumann (Germany) Gordon Munro (Denmark), and Stafford Lightman, Jonathan Seckl, Colin Ingram, Alison Douglas, Simone Meddle and Paula Brunton (UK).

This Festschrift was supported by The Physiological Society, The British Society for Neuroendocrinology, The International Neuroendocrine Federation, The Sharpey–Schafer Endowment Fund of the School of Biomedical Sciences of the University of Edinburgh and Wiley-Blackwell, the publishers of the *Journal of Neuroendocrinology*.

The fabulous day of interesting talks finished with a splendid dinner and an entertaining dinner speech given by Gareth Leng.

### Mike Ludwig

PS: If you are wondering, John has not retired yet, he will formally retire from the university at the end of next year but we all hope that he is with us for many years to come.

### The Journal of Physiology impact factor rises

The 2008 impact factor for *The Journal of Physiology* has been revised upwards from 4.605 to 4.649, as a result of a re-count of source articles used in the calculation of the factor. Until another metric is accepted by the research community as a good indicator of where to publish, the IF will continue to be an important element in the journal's strategic planning.

## Physiology 2009 – Dublin

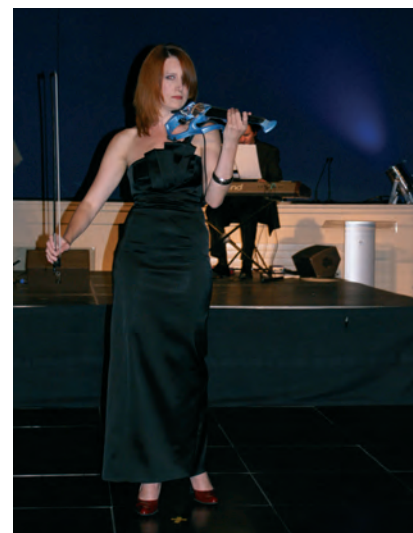
This is the brief report of one local organizer of the Main Meeting of The Society held in Dublin in July.



It was a particular pleasure to welcome old friends and new guests to the new Medical School on the main campus of University College Dublin. With the passage of time some memories are still imprinted strongly. Many physiologists were seduced by the new methods of genomic manipulation which are becoming more sophisticated than the simple one gene knock out approach, which resembles a simple nineteenth century ablation experiment. And so this is what I have brought away from Dublin 09:



John Coote (left) and Andy Ramage in the O'Reilly Hall (which according to Andy is as pointless as calling a similar building in the University of Cardiff the Jones Hall). Photograph by Tim Ford, University of Nottingham.



Musical entertainment after The Society's dinner. Photograph by Tim Ford.

*There is nothing as powerful as an idea whose time has come.* The merger of sophisticated genetic manipulation and optical signalling should open new areas of exploration.

The dinner was held in The Mansion House which is the residence of the Lord Mayor of Dublin. The Meetings Secretary, Prem Kumar, reached new heights in stand-up comedy and he was followed by a sexy violinist.



Prem Kumar (left) and Jeremy Ward (right) with Colin Nurse who delivered the Michael deBurgh Daly prize lecture.

The organizers of the many symposia held in Dublin are very pleased with the positive feedback that they received from their guest speakers and audience. I wish to express my sincere thanks to The Physiological Society team for running the event so smoothly that I could sit back, forget I was involved at all and just enjoy it.

**James FX Jones**

## IUPS Kyoto 2009

July 28th–1st August

When Kyoto was confirmed as the venue for the 36th IUPS Congress, I wondered why there. I now know why.

I arrived a week ahead of the IUPS Congress, to attend the International Symposium on Exocrine Secretion (ISES), being held in the University of the provincial city of Tokushima. Attending the symposium would give me my first ever taste of Japan, in more ways than one. I arrived in Osaka and was immediately struck by how clean and ordered everything was and how little the English language was used. Despite my appalling inability to speak Japanese everybody was extremely courteous and helpful and I was duly put on the 4.10 pm (and I mean 4.10 pm) bus to Tokushima. Communication difficulties certainly created a few amusing situations over the most basic of things and I became very good at 'Charades'.

Adjusting to the time difference was an initial problem, with me waking up at all hours of the night; however, the ISES meeting helped me to get my brain into gear and focus on the excellent science that was presented in Tokushima and soon to be at the IUPS Congress.

A bus took the ISES participants to Kyoto for IUPS, via numerous stops to introduce those of us unfamiliar with Japanese culture to such things as traditional dancing, indigo dyeing, Japanese puppet theatre and the famous Naruto whirlpools, which we would otherwise not have seen.

The Congress was in the Kyoto Conference Centre, located in beautiful surroundings. The opening ceremony was in the main hall and included, as well as the formal speeches, examples of traditional Japanese culture. Unfortunately, no cameras were allowed, for security reasons, as the Japanese Crown Prince was attending. Perhaps this was the reason why the registration desk was chaotic on that first morning. The main hall

looked familiar and it dawned on me that the Kyoto Protocol on Global Warming had been signed there. Historic surroundings indeed!

The Congress was well organised and the sessions were all near at hand. The science presented was excellent and included something for everyone. Many younger scientists were given the opportunity to present their work orally, which I felt added to the many good aspects of the meeting. There was also an excellent array of posters on display each morning and afternoon and a good number of commercial companies were represented, which, considering the economic climate, was no mean feat.



Local youth groups and school students provided lunchtime and evening reception entertainment. Clearly – 'Japan has talent'! The Taiko drummers at the Welcome Reception were fantastic and had the audience enthralled.

The hospitality of the ISES and IUPS hosts was excellent. In the UK, I was

not keen on sushi; however, it is hard to avoid eating it in Japan and after a few days I was an enthusiastic convert.

For me the Congress was a memorable one. I left the meeting having learnt new things, met old friends and made new ones, got new ideas and formed new collaborations.

My abiding memories of Japan are too numerous to mention in full. However, Kyoto is an interesting place to visit and I found the Japanese people exceptionally polite and friendly and I would recommend Japan as a country worth visiting. I would readily go back on holiday to explore it!

Now roll on IUPS 2013 Birmingham.

**Douglas Bovell**

## More on IUPS 2009

Set in the beautiful and historical city of Kyoto, the IUPS Congress was a conference brimming with wonderful science and extraordinary culture. The meeting was opened by the newly elected President of IUPS, Denis Noble and the opening ceremony was attended by His Imperial Highness, the Crown Prince of Japan. The attendance of one of the Imperial family at the meeting adds emphasis to how Japan as a country values strong scientific focus. One thing I didn't know until the opening speech was that the Imperial Palace has its own research laboratory which carries out marine research. The lab was originally opened by the grandfather of the Crown Prince.

To find a more cultural experience as a backdrop to a conference is hard to imagine than in Kyoto. The city of Kyoto itself is enriched with 17 World Heritage Sites including the Kamigamo-jinja Shrine and the To-ji Temple. Within the conference, daily entertainment in the form of traditional Japanese dance and music entertained everyone. The traditional lion dance or Shishi-Mai, performed by local school children





was wonderful. The coordination and precision of the timing to achieve the dance inside the costume lion must take months of practice, not to mention extreme physical fitness.

The array of symposia was amazing. One interesting symposium I attended was on the subject of brain-machine interfaces as ways to repair connections within the nervous system, chaired by Mitsuo Kawato of ATR Computational Neuroscience Laboratories, Japan and Tetsuya Yagi of Osaka University, Japan. This symposium to me reflected how far physiology is moving in terms of piecing things back together as described by Professor Noble.



Top, the Golden Pavilion (Kinkakuji) in Kyoto, and bottom, reception put on by the Canadian IUPS 2013 bid team. The ice sculpture is the CN Tower in Toronto.

Alongside the science and entertainment, there were also some themed symposia on other aspects of science including equal opportunities, ethics of research

and public outreach. A half-day symposium on Women in Physiology was sponsored by Shiseido Co. Ltd, the Japanese cosmetics company. In 2008, *Nature* reported that the proportion of women in science in Japan was just 12.4% and that only 1/87 Japanese universities had a female president (*Nature* 451, 865). But in Japan, they are trying to change this with new grants and support networks for female scientists. At the symposium experiences of female scientists from China, India, Japan, the UK and USA were presented and included personal accounts, hurdles to overcome and also triumphs. At the 'Beyond Gender' social event after the symposium, Shiseido samples were given out to all attendees – it was science slowly approaching other industries – our version of the Oscars afterparty! Not to be too feminine but I am all for make-up samples at conferences – Birmingham 2013 take note!

**Fiona Randall**

### An introductory workshop on human and clinical physiological techniques

10–11 December 2009, King's College London and Imperial College London

Speakers include:

**Steve Harridge** (King's College London, UK)

*Techniques in human muscle physiology*

**Mike Grocott** (University College London, UK)

*The human body at high altitude*

**WgCdr Nic Green** (Royal Air Force)  
*Acceleration and the body. Physiology of flying fast jets*

**Mike Tipton** (Portsmouth University, UK)

*The human body in cold water*

**Kyle Pattinson** (University of Oxford, UK)

*Getting inside the black box, what can we learn from MRI?*

**Angela Atalla** (Imperial College London, UK)

*Integrated physiology in a clinical context: understanding heart failure*

## Cellular & Integrative Neuroscience

After a break of 11 years The Physiological Society is returning to Cardiff to hold a themed meeting on Cellular & Integrative Neuroscience, 14–16 December, 2009



### Speakers

**Gary Lewin** (Max-Delbrück Center, Berlin, Germany)

**Helen Kennedy** (University of Bristol, UK)

**Hugh Matthews** (University of Cambridge, UK)

**Hiroaki Matsunami** (Duke University, Durham, USA)

**Maria Fitzgerald** (University College London, UK)

**Adam Sillito** (University College London, UK)

**David McAlpine** (University College London, UK)

**Matteo Carandini** (University College London, UK)

**Andrew King** (University of Oxford, UK)

**Irene Tracey** (University of Oxford, UK)

**Edmund Rolls** (Oxford Centre for Computational Neuroscience, UK)

**Pieter Roelfsema** (Netherlands Institute for Neuroscience, Amsterdam, The Netherlands)

**Bridget Lumb** (University of Bristol, UK)

**Matt Diamond** (SISSA, Trieste, Italy)

**Peter Brennan** (University of Bristol, UK)

**Jens Schouenborg** (Lund University, Sweden)

**Michael Brecht** (Bernstein Center for Computational Neuroscience, Berlin, Germany)

**Daniel Wolpert** (University of Cambridge, UK)

## A week in the life of... a neuroscientist comedian

In my experience, if you tell a stranger you're a neuroscientist, they react with a mixture of surprise, admiration and suspicion. Tell someone you're a comedian, they respond in the same way but in a more exaggerated manner. Tell someone you're a neuroscientist comedian, they simply dismiss the ludicrous statement and start discussing the weather

My desire to entertain is something of a family trait, but my skewed world view and overly analytical mind has always resulted in me being drawn to science, which is why I'm completing my PhD in Behavioural Neuroscience. Many comedians started off as scientists (Dara O'Briain, Harry Hill, etc.), but very few have tried to combine science and comedy, with (as I've discovered) good reason. But I persevere and, slowly, it seems to be working. It's impossible to describe my experiences and career structure fully in a short article, so here's a rundown of a typical week in my life.

**Monday:** Monday usually begins with checking my experimental subjects: weighing, monitoring health, food levels, etc. My family still thinks being a neuroscientist is a glamorous occupation. If this is the case, a morning being scratched, bitten and defecated on by three dozen rats should keep me grounded. After this, I do more work on my next experimental set-up, performing cutting-edge research armed with a large box, some old Christmas decorations and a packet of coco-pops. The glamour is almost intoxicating at this point.

In the evening, I try out some new material at a comedy gig. Backstage I mention that I work with animals and another act gets very aggressive and says, I quote, 'You'd better not do any of that near me, I'm a vegetarian.' The inanity of this statement leaves me dumbstruck.

**Tuesday:** Have to go over results from an earlier experiment, trying to find a significant pattern in disappointing data. Before starting my PhD, I had never come across the statistics package SPSS, and I sometimes long for those days of carefree optimism. For those unfamiliar with SPSS, it reminds me



of the NHS: we'd be lost without it, but that doesn't mean we don't hate it.

That evening I host the regular Student Union comedy night. I mention my comparisons between SPSS and the NHS. Unfortunately, the 30 or so Art and History students in the front don't know what I'm talking about and assume that SPSS is something to do with the police. Comparing one government institution with another really doesn't have the same impact, but my wife later points out that the original joke wasn't funny either, so no real loss there.



**Wednesday:** Surgery day. It's an unavoidable aspect of modern science that animal experimentation remains necessary, and that a study of the function of specific brain regions requires lesioning or physical disruption. I've had to point out to anti-vivisectionist 'friends' that just because scientists do it, it doesn't mean we enjoy it in any way. This is true, as performing a neuroanatomical lesion with any degree of accuracy takes several hours of concentration at a time. If nothing else, it's boring. This revelation makes me chuckle, but I decide I really shouldn't mention it if I'm ever asked to write a magazine article.

No comedy tonight, but I run some new material past my wife. The look she gives me is similar to the one I give a rat that urinates on my sleeve.

**Thursday:** Receive several replies to job applications for post-PhD positions – all rejections. One rejection is from a job I never applied for, which does damage the motivation somewhat. After much deliberation, I decide to remove the 'comedian' section from my CV – just doesn't look right on an academic application. Spend another 8 hours performing brain lesions. My careers advisor told me I'd 'never be a brain surgeon'. She was half right, I guess.

In the evening, I fill in for a last-minute drop-out at a lovely gig I know. A French woman in the front row looks confused, so I convert all my jokes to metric and she starts laughing. I mention how nonsensical the excuse 'big bones' is for being overweight. A woman laughs and explains she used to be big boned. Reflexively, I ask how long she spent on the International Space Station, then have to spend 5 minutes explaining how prolonged



periods of low gravity can lead to bone loss due to calcium depletion. Make a note: it's important to know your audience, and the people of Abergavenny aren't really up to speed on the effects of prolonged microgravity on human skeletal structure.

**Friday:** Today is important – it's my first ever attempt at a science-themed comedy night. 'Humourology', as I've dubbed it (an off-the-cuff suggestion I don't like but which seems to have stuck), is a night of as many comics as I can find performing material based on and with reference to complex science, hosted by me. I manage to focus on my PhD work, but am also illicitly using the photocopier for flyers, which I hope nobody discovers. By the time the show starts that evening, there are over a hundred people in attendance. Science comedy is clearly an untapped niche. The whole thing goes incredibly well, particularly my analysis of the scientific inaccuracies of classical jokes. The night wraps up around 11 pm. After promising to do more *Humourology* in the near future, I go home and pass out, dreaming of the stardom that is surely to come my way after the success of tonight.

**Saturday:** Have to go into the lab to start a testing session. Luckily, spending several hours staring at rats in a box undermines my delusions of grandeur.

**Sunday:** Same as Saturday, but with a later start as I forget my lab access card.

So there we have it: a typical week in my life. Not a normal sort of daily existence I admit, but I do get a certain satisfaction knowing I'm probably the only person in the country experiencing it and I persevere, as I enjoy combining science and comedy. If anyone does require my services, in either a neuroscientific or comedic capacity, please feel free to email me at [humourology@live.co.uk](mailto:humourology@live.co.uk)

**Dean Burnett**

## Understanding ion channels and their role in brain disorders

On a recent trip to Seattle Angus Brown took the opportunity to catch up with Professor Bill Catterall, to talk about his pioneering work in the field of voltage-gated ion channels and to discuss ongoing work in the field of epilepsy

**Angus Brown (AB).** Where did you carry out your undergraduate and PhD degrees?

**Bill Catterall (BC).** I grew up in Rhode Island and completed my bachelor studies in Chemistry at Brown University. From there I went to Johns Hopkins School of Medicine in Baltimore where I received a PhD in physiological chemistry. My thesis work was on the structure and function of F1-ATPase, the mitochondrial enzyme that makes ATP, a long way from my current research interests.

**AB.** You worked with Nobel Prize laureate Marshall Nirenberg at the NIH. What was it like working for a Nobel Prize winner that early in your career?

**BC.** Well, all three of my mentors had important influences. Pete Pedersen, my PhD supervisor at Johns Hopkins, was really crucial in teaching me about the basics of science – how to develop a critical hypothesis, to design an experiment to critically test a new idea, to design the right control experiments, and to have the work ethic of science. Marshall was influential in two equally crucial ways. First, he taught me how to identify a big problem to work on. He liked to say 'all science is difficult, and all experiments are hard to get to work, so make sure you're working on something important'. And he introduced me to neurobiology, which I had not known very much about before going to his lab. My third mentor was my Departmental Chair at the University of Washington, Ed Krebs, who taught me about academic administration. He used to say 'always take administration as a hobby', by which he meant that he didn't want administration to crowd out his research and the other aspects of his academic life, and I have followed his example and tried to balance teaching, administration and research.



**AB.** Which scientists inspired you in your early days?

**BC.** In my undergraduate and graduate training, I read textbooks by Bernard Katz, on synaptic function, by Sol Snyder, on neurotransmitters and neurotransmitter receptors, and by Pedro Cuatrecasas, who was studying hormone receptors with new chemical biology approaches. I found their work quite inspiring in turning me toward neurobiology for my postdoctoral research. Later, the work of Jean-Pierre Changeux and Arthur Karlin on acetyl choline receptors was very influential for me because they were the first receptor proteins to be characterised using biochemical techniques. Since I'd been trained in biochemistry, I was excited about applying those methods to voltage-gated ion channels. I was also influenced greatly by the work of Hodgkin and Huxley in my choice of research problem. Understanding how the sodium channel that they defined functionally could work at the molecular level really captured my interest.

**AB.** When did you become aware of their work?

**BC.** Not until I was a postdoctoral fellow, because that's when I became interested in neuroscience and then in sodium channels. When you become interested in sodium channels, you immediately look back to the work of Hodgkin and Huxley that began

the modern era of research on ion channels. I decided what I wanted to do when I set up my lab was to apply membrane biochemistry methods to voltage-gated ion channels, to which they hadn't been applied before.

**AB.** Not all of our readers may be familiar with all the details of ion channels, so could you tell us a little about voltage-gated channels? What was the common ancestor and what were the evolutionary forces that resulted in the appearance of sodium, potassium and calcium channels?

**BC.** We've learned in recent years that sodium and potassium channels are present in bacteria, and that they are important in regulating ion fluxes across the cell membrane in response to the bacterial membrane potential. Calcium channels first appear in eukaryotes, in yeast, and they emerged at the time that calcium-based signalling became important. Electrical signals by sodium and potassium channels control calcium entry, and calcium in the cytoplasm regulates many different processes. Even a cell as simple as yeast contains calmodulin and has many calcium-dependent regulatory processes, so I see the development of calcium signalling as a key step in ion channel evolution.

The next big step in ion channel evolution is in metazoa, the multicellular organisms. Signal transduction is more complicated in metazoa in order to control many cells in an organised way, and ion channels evolved to allow that higher level of control. One of the key steps between the single-cell organisms and metazoa was the development of action potentials driven by sodium channels, which are used in metazoa to signal over long distances. A very early example is the sodium-dependent action potential in the nerve net of jellyfish. Finally, in vertebrates electrical signalling becomes faster, more precise, more diverse, more important, and there are a lot more ion channels. For example, there are 10 sodium channels and 10 calcium channels in mammals compared to one or two sodium channels and three calcium channels in most of the invertebrates whose genomes I've looked at.

**AB.** You've been involved in research in ion channels since the early 1970s. One thing that I think is very important is that people in your position, who have been intimately involved in the field for several decades, have a key insight into the development of that field. So from the perspective of 30 years could you describe where the field was when you became involved and what have been the key advances in the field over the years?

**BC.** I'll give you my personal perspective, but I am sure others in the field would have different highlights. The first advance that I would highlight, which we contributed to, was discovery of the ion channel protein molecules themselves. When I entered the field in 1972, there was a well-developed understanding of the ionic currents that generate the action potential, but there wasn't any understanding of what ion channel molecules were like. Most people assumed they were protein molecules, but there was a respectable school of thought that electrical excitability may be due to membrane phospholipids. The idea that sodium conductance was mediated by an ion channel with a selective pore was first presented clearly in the literature by Bertil Hille. He argued that to explain the high level of sodium flux compared to the apparently small number of channel molecules involved in sodium conductance, it was necessary for the permeability pathway to function as a pore rather than as a transporter. That turned out to be a very insightful proposal, which was confirmed much later by single channel recording and eventually by three-dimensional structure determination.

When I began to work on sodium channels with Marshall Nirenberg, the key information that seemed to us to be missing in the ion channel field was an understanding of the molecules that form the pores, so we developed neurotoxins as specific probes of sodium channels and used them in biochemical experiments. We measured neurotoxin binding and sodium ion flux in neuroblastoma cell lines that Marshall had developed, which expressed sodium channels

in cell culture. Following my move to the University of Washington, I built on those experiments by using neurotoxins to identify and purify the sodium channel protein from mammalian brain and later by using similar approaches to purify the calcium channel protein. These were exciting experiments for us at the time because they gave us the first glimpses of ion channel protein molecules. This advance was also important in changing the focus of the field from studying ionic currents to characterising the molecules that were generating the ionic currents, and that's remained a primary focus of the last 30 years in ion channel research. It's amazing to me that there are 143 proteins in the human genome related to sodium and calcium channels and that the ion channel protein superfamily is one of the largest families of signal transduction proteins. G protein-coupled receptors and protein kinases number in the range of several hundred, and then ion channels and G proteins number in the range of 140 to 150 as the next most prominent signalling proteins. So it's really a very important and very large family of signalling molecules that emerged from experiments aiming to determine what the ion channel protein molecules look like.

A second key realisation over the past 20 years is that ion channels aren't just involved in electrical signalling in nerve and muscle, but they're involved in virtually every aspect of cellular regulation – in epithelial cells, in endocrine cells, even in lymphocytes. In fact, it turns out that potassium channels and calcium channels are even crucial in sperm and eggs. It really is remarkable that, from a beginning in highly specialised excitable tissues, it's now clear from the work of hundreds of scientists that this signalling system is involved in almost every aspect of cell physiology. Of course, that's why 143 proteins are needed.

The third advance that I would highlight is the realisation that ion channels are involved in a wide range of diseases. None of us would have predicted in the 1970s and 1980s that there would be dozens of genetic



diseases caused by mutations in ion channels. Ion channelopathies have steadily grown in number, and grown very much in importance in advancing how we think about the broader non-genetic forms of these diseases. For example, inherited epilepsy is very rare, but studies of genetically based inherited epilepsies have given many new insights into more widespread forms of this disease. It's even more true in the heart, where cardiac arrhythmias that are genetically based are quite rare, but they have given very important insights into the more common types of cardiac arrhythmias that afflict a large number of people. I think this has been a very important development in understanding complex diseases, and the ion channelopathies now include endocrine abnormalities, kidney misfunction, immunodeficiency and several other classes of disease.

**AB.** It seems to me that the focus of ion channel research has moved away from purely sequence-based studies and is now focussing on the relationship between structural aspects of ion channels and function. I'm thinking in particular of your work on sodium channels and tenascin, and calcium channels and synaptic vesicle components. Is this the case?

**BC.** It was a surprise in our earliest biochemical experiments to realise that the ion channels are multi-subunit proteins. It didn't seem obvious to us that multiple types of subunits would be needed for proteins to form a pore. We found in our early biochemical experiments that ion channels are formed from two classes of subunits – pore-forming subunits that are related for all members of the ion channel superfamily and auxiliary subunits that differ for each ion channel type. The auxiliary subunits are integral members of ion channel protein complexes. Moreover, there are many more proteins attached, so that ion channels form signalling complexes containing many different proteins. I think of the functional consequences of the activity of ion channels as local. When a single sodium channel opens, the depolarization that it causes is local. When single calcium channels open, a local microdomain of high calcium

forms, so the intracellular calcium signal is also inherently local. The best way to have proteins respond to the local change in membrane potential, or the local calcium signal, is have them bind to the ion channels, and we now know of dozens of proteins that are bound for this reason. In the case of sodium channels, there are cell adhesion and extracellular matrix molecules like neurofascin and tenascin and cytoskeleton molecules like ankyrin that are important in putting and keeping sodium channels in the right place. In addition, there are a whole host of signalling molecules – kinases, phosphatases, calmodulin and G proteins – which all bind to sodium channels and regulate their properties.

In the case of calcium channels it's an even more well-developed story. Not only are there extracellular matrix and cytoskeletal proteins, cell adhesion molecules, kinases, phosphatases, calmodulin and G proteins, but the SNARE proteins and SNARE-binding proteins that are involved in exocytosis at nerve terminals and in secretion in other cell types also bind to calcium channels. An exceptional example of formation of a multi-protein ion channel signalling complex is provided by a recent proteomic analysis of the proteins associated with the presynaptic calcium channel by Bernd Fakler and colleagues. Their work showed that more than 100 proteins are specifically associated with presynaptic calcium channels. Unbelievable! Within those 100 proteins are the many calcium channel-associated proteins that we already knew about, so it was comforting to know that the one-by-one protein approach is providing correct answers. I think the right way to think about ion channels is at the centre of a large complex of proteins engaged in a very complicated function.

**AB.** One thing that sticks in my mind in reading Hodgkin's autobiography is his sense of frustration in that, despite winning the Nobel Prize for his work on action potentials, he was unable to help the legions of people with neurological conditions that contacted him in the hope of a cure for their maladies. What do you think

will be the key advances that will allow such progress?

**BC.** I agree with Professor Hodgkin that it is frustrating that one can't do more, but in the years since the 1950s many advances have been made. We have new generations of local anaesthetics, anticonvulsants and antiarrhythmic drugs that are targeted at sodium, calcium or potassium channels. We have the whole evolution of calcium channel blockers as drugs that are very important in cardiovascular disorders like arrhythmias, hypertension and angina, as well as calcium channel blockers for control of neuropathic pain. I think we have the opportunity for even greater progress in this area because few of the drugs in the clinic have taken advantage of the knowledge of the 143 different members of the ion channel superfamily provided by the sequencing of the human genome. One could make these drugs more selective with fewer side effects if we could target individual ion channels. That is a major effort in drug companies now.

**AB.** Could you tell us more about your work on the Na<sub>v</sub>1.1 mutant and its role in human epilepsy? It seems paradoxical that a loss of function mutation of sodium channels would lead to hyperexcitability.

**BC.** You bring up a project that's relatively new in our lab and one that's been very rewarding for me and for my colleagues. As I said before, one of the major developments in our field was the discovery of ion channelopathies beginning in 1990. About 5 years ago, we were struck by a particular ion channelopathy called severe myoclonic epilepsy of infancy (SMEI), which is a very severe form of paediatric epilepsy that results in severe seizures, permanent mental retardation and cognitive deficit, and other serious co-morbid problems for the children who have it. And as you point out, this was a paradox. It seemed to us that the loss of function mutations in sodium channels that cause the disease should result in a reduction in brain electrical activity rather than an increase in excitability, so we decided to study this disease by making a mouse genetic model. To our surprise, we found that these mutations cause

a dramatic loss of sodium channel function and electrical excitability in the GABAergic inhibitory neurones in the hippocampus without much effect on the electrical excitability of the excitatory neurones. The brain operates on a balance of excitatory and inhibitory inputs. When the inhibitory neurones are prevented from generating action potentials, and releasing the inhibitory neurotransmitter GABA, the excitatory neurones have a party and hyperexcitability and epilepsy result. We're excited that we've been able to add some new understanding of the pathophysiology of this devastating disease. We're now trying to conduct 'mouse clinical trials' with different drug combinations than those that are used in current therapy of this disease, realising what its causes are, in order to find drug therapies that would be more effective in preventing seizures and the other co-morbidities.

**AB.** Is there any significance to the fact that as well as epilepsy, the condition affects the cerebellum; there is this ataxia associated with it which you see in the children, but which also occurs in the mouse model? Does this mean that what occurs in the mouse exactly mirrors the human condition?

**BC.** Well, we feel very fortunate that our mouse model mimics the human disease in all of its parameters. Children with this disease have several accompanying co-morbidities, including ataxia. Another even more important co-morbidity is cognitive decline, which is dramatic in these children. They have normal cognitive function and normal developmental achievement until their seizures begin about 6 to 9 months of age. Between year 1 and 2, they typically reach a plateau in their cognitive and psychomotor development, and between years 2 and 5 they often decline and lose developmental milestones that they have gained before. Other less devastating but scientifically interesting co-morbidities include sleep disorder and hypersensitivity to light, and amazingly, our mice have every one of these co-morbidities, so they are a remarkably good model of the disease.

**AB.** Obviously multiple areas of the brain are being affected – cerebellum,

hippocampus, cerebral cortex and various others.

**BC.** We think that each of the co-morbidities is caused by failure of firing of a different class of GABAergic neurones. In the case of ataxia, we have shown that the cerebellar Purkinje neurones, which are crucial for control of movement, have a huge impairment in their sodium currents and action potential firing capabilities in the mutant mice, so that's the likely source of ataxia. Of course, GABAergic neurone functions in the cerebral cortex and hippocampus are crucial for learning and memory, so we think that the cognitive defect is caused by two interacting factors: the failure of GABAergic neurone function, which by itself should be sufficient to cause cognitive deficit, as well as cell death and loss of neurones due to the seizures that also must contribute to cognitive deficit. We're actively studying that process.

**AB.** So that must be a very difficult clinical problem because you can imagine if it were hyperexcitability of sodium currents – if it was too large it would be fairly easy to knock it down, but how do you get the sodium current to increase, do you try to increase the open probability?

**BC.** Well, we think that the problem is failure of GABAergic transmission. Since there isn't a good way to upregulate sodium channel activity in a selective way, we think the right approach is to upregulate GABAergic transmission, so that the lesser amount of GABA that is released has a greater impact. We also think this is a good approach because the GABAergic neurones will try to fire at the right times in appropriate physiological or cognitive context, so enhancement of their activity should be therapeutically useful. We're trying combinations of drugs that increase GABAergic neurotransmission in multiple ways by enhancing the postsynaptic response of GABA receptors with benzodiazepines, by enhancing the amount of neurotransmitter GABA that remains in the synaptic cleft by blocking its reuptake into the nerve terminal, and by increasing the amount of GABA in the nerve terminal by blocking its metabolism by the enzyme GABA

transaminase. We're hoping that drug combinations that aggressively enhance GABAergic function will have a positive impact to prevent seizures, reduce co-morbidities, and prolong life in mice. We're trying to optimise these treatments and study their effects on co-morbidities to see if they also are improved.

**AB.** I look forward to reading those papers.

**BC.** Well, it's exciting for us because we haven't come close to having a direct impact on a disease in our research before. Now we may be able to do that and resolve a little of the frustration that was expressed by Alan Hodgkin, which we also feel because we have so much new information, but not yet any really new therapies.

**AB.** Recently you were inducted into the Royal Society in the UK. What does it mean for an American to be inducted into the hallowed halls of Newton, Darwin etc?

**BC.** Well, it is a great honour to be inducted into the Royal Society, which holds a very special place in my mind for a number of reasons. First, I have 100% English ancestry, so it's very nice to be recognised in the home country. Second, as we've mentioned, the founders of our field were members of the Royal Society – Hodgkin, Huxley, Katz and many others. In fact, at the induction ceremony at the Royal Society I was honoured to present my summary of our work at a podium under a picture of Andrew Huxley, so I could say that our work derives from the discoveries of this exceptional member of the Royal Society. Finally, there are relatively few foreign members of the Royal Society, and it's a great honour to be included with them. I'm still learning about the opportunities that foreign membership in the Royal Society presents for advancement of science in the UK and around the world.

**AB.** Will we be seeing more of you in Britain?

**BC.** Well, it's a long flight, as you well know, but I will try to visit more often, as I now have a good B & B in London since members can stay at the Royal Society.



## Letter from Japan 3 – Embracing a new culture

I am now 8 months into my first postdoctoral position – where has the time gone? Life is starting to feel normal here. The experience of moving to a new country made the time go by like a whirlwind. The whole thing has been an emotional rollercoaster in the least negative way. Being so far away from familiar things means that you do have moments when you feel the distance but then the excitement of constant challenges of communication and life in and out of work keep you on your toes. Being in a new lab and a new life was so exciting it was actually difficult to focus at times and the need to make friends meant I never said no to any invitation to socialise. I felt I was totally happy but was worried the bubble would burst if I stopped and got lonely – I am sure that is an anxiety most people have when they move to a new place so far from familiar things. I have now lost that feeling and can relax – I have a good group of friends and am not scared anymore that it might go wrong. Now I am settled and things are calmer I have started to take up new hobbies. Having had horses all my life I am used to being constantly occupied when not at work, especially at the weekends. There is a place to ride here but it is so hot I didn't fancy it but needed something to keep me active and outside. The scuba diving here is amazing and I have taken my PADI course. I tend to dive once or twice a week. You see the most amazing tropical fish and the coral is so close you can literally rent a tank and walk in from the shore, or go on a boat to one of the many surrounding islands.

I have just had my mum and friend over to visit which really reaffirmed to me how special a place Okinawa is. I got to take some time off and explore the island more than I have so far. When you are working all week and the sun is shining at the weekend it is tempting to lie in it. There is a vast amount of history



Me and my fellow classmates (Venkatesan Satish from India and Kun Gao from China) trying traditional summer dress with our Japanese teacher, Yamauchi-sensei.

here, both pre- and post-Second World War. There used to be castles all over the island but sadly most were destroyed in the Battle of Okinawa. Some have been restored, at others you can explore the ruins. The horrendous stories of what the Okinawan people endured in the invasion are hard to take when you consider the beauty and tranquillity of the island today. The Peace Park on the south coast of the island is really breathtaking. Set on the edge of high cliffs with the sound of breaking waves, it is a memorial to all those lost in the battle from all over the world and a beautiful message from the Okinawan people about the importance of peace. It is hard to believe how few people have heard of Okinawa.



An Okinawan butterfly at the Ryukyu Butterfly Park.

Things in the lab are really exciting just now. We have two new postdocs in the group which adds to the enjoyment of work – more minds, more ideas, more brainstorming. We all work on fairly independent projects and are setting up new things so that can be stressful when it all takes time but the discussions are stimulating and the

team atmosphere is great. We are getting ready to head to Chicago for the annual meeting of the Society for Neuroscience as I write this so have been poster making. I miss the lab at times like this. However, it is amazing after writing a thesis, how short a time a poster seems to take. How your ideas change as you progress. I hope one day paper writing will seem quick! I am in the process of doing that just now.

The university encourages integration into Japanese culture and recently we've had the opportunity to take part in local events such as the Obon and EISA festivals. Both these festivals included lots of traditional Japanese dance and parades and were amazing to see. Even better, I got to try a kimono. I have now taken the beginners' Japanese class provided by work and am finding it much more simple to get by with the few words I know. Being able to read a few symbols can also be great as some menus in restaurants don't have an English version here. I am happy to try most things but I don't want to stretch to the local delicacy of pigs' ears!

### Fiona Randall

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## Excitation-dependent $\text{Ca}^{2+}$ influx in vertebrate skeletal muscle is in, again

An influx of extracellular  $\text{Ca}^{2+}$  into skeletal muscle excited by action potentials was originally reported in the 1950s. At least three distinct  $\text{Ca}^{2+}$  entry pathways across the transverse tubular system of working skeletal muscle have since been identified. The recently discovered action potential-activated current appears to be the pathway responsible for the excitation-dependent  $\text{Ca}^{2+}$  influx but its specific physiological roles remain speculative

Skeletal muscle cells in vertebrates, when compared with cardiac muscle cells, evolved to be able to deliver calcium for the activation of the contractile apparatus in a faster and more precise manner, in order to suit completely different functions in the body. In cardiac cells there is a fundamental need for  $\text{Ca}^{2+}$  influx to trigger the cascade of events that lead to contraction in the process known as excitation–contraction coupling (EC coupling; Bers, 2001). In contrast, work from Lüttgau's laboratory in the 1970s showed unequivocally that skeletal muscle could twitch and develop tetanic force in the absence of extracellular  $\text{Ca}^{2+}$ . This represented a major deviation from the physiology of the cardiac cell. Nevertheless, Bianchi & Shanes showed in 1959 that an influx of  $\text{Ca}^{2+}$  into skeletal muscle occurred during excitation by measuring  $^{45}\text{Ca}^{2+}$  entering a muscle after a couple of hours of low-frequency stimulation. This observation was confirmed by others over the next three to four decades, but a precise role of this excitation-dependent  $\text{Ca}^{2+}$  entry in skeletal muscle cells was not defined by Bianchi & Shanes or the other researchers. Although no argument can be made for a specific requirement of extracellular  $\text{Ca}^{2+}$  to produce force in skeletal muscle, if one were to look closely at some of the force traces presented in the work published by Lüttgau & Spiecker (1979), one could notice that a smaller initial force level was achieved at the beginning of a tetanus in the absence compared to the presence of extracellular  $\text{Ca}^{2+}$ .

At least three distinct  $\text{Ca}^{2+}$  entry pathways are known across the transverse tubular (t) system membrane of skeletal muscle fibres that could be functional during periods of work and responsible for



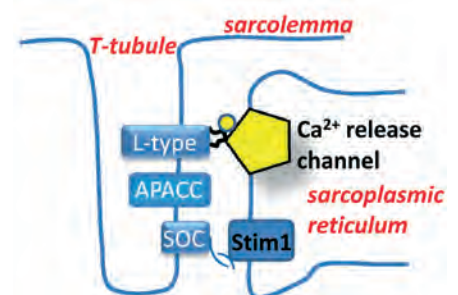
From top left clockwise: Bradley Launikonis, Oliver Friedrich and George Stephenson

the influx described by Bianchi & Shanes (1959; Fig. 1).

The L-type  $\text{Ca}^{2+}$  channel is activated during square depolarizing pulses. The resulting slow, inward  $\text{Ca}^{2+}$  current is easily detected with conventional electrophysiological techniques (Melzer *et al.* 1995) and this is perhaps the reason that this current is so well described, at least biophysically. It has been assumed that a high frequency of action potentials in skeletal muscle may be equivalent to chronic depolarization, to induce  $\text{Ca}^{2+}$  influx through the L-type channel. However, experimental evidence for this in adult mammalian skeletal muscle is hard to find. Indeed, chronic depolarization and a high frequency of action potentials induce very different electrical waveforms across the t-system, highlighting the need for the current to be examined under more physiological conditions. This makes it most unlikely for the L-type  $\text{Ca}^{2+}$  current to be responsible for the  $\text{Ca}^{2+}$  influx measured in the experiments of Bianchi & Shanes.

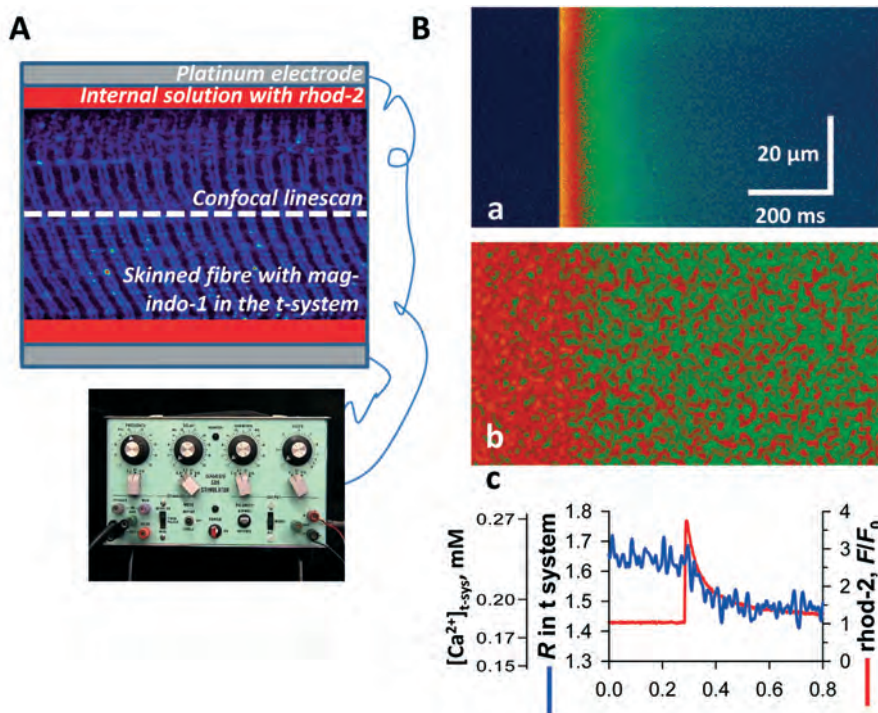
Furthermore, a chronic depolarization of muscle in the presence of the specific L-type channel blocker nifedipine only

reduces the  $\text{Ca}^{2+}$  influx by a small amount when the SR  $\text{Ca}^{2+}$  is low (Kurebayashi & Ogawa, 2001). This means that other, more significant  $\text{Ca}^{2+}$  influx pathway(s) are activated during a depolarization when the SR  $\text{Ca}^{2+}$  is low. In their paper, Kurebayashi & Ogawa describe a store-dependent  $\text{Ca}^{2+}$  influx into skeletal muscle. Using chronic depolarization via ionic substitution of the external bathing solution, they show that most of the  $\text{Ca}^{2+}$  in the SR needs to clear SR in order to induce the store-dependent current. In non-excitable cells  $\text{Ca}^{2+}$  must be lost from the cell to induce store-operated  $\text{Ca}^{2+}$  entry (SOCE). However, in skeletal muscle this is not likely to occur physiologically. In skeletal muscle,  $\text{Ca}^{2+}$  within SR needs only to drop to levels that cause  $\text{Ca}^{2+}$  dissociation from the  $\text{Ca}^{2+}$ -sensing protein, Stim1, located in the SR membrane (Fig. 1).  $\text{Ca}^{2+}$  released from the SR during muscle contraction binds to cytoplasmic buffering sites, causing transient  $\text{Ca}^{2+}$  depletion of the SR. Thus, a situation can occur during periods of intense



**Figure 1.**  $\text{Ca}^{2+}$  channels at work in the transverse (t) tubules. At least three  $\text{Ca}^{2+}$  channels are known to be active during periods of work in skeletal muscle: L-type  $\text{Ca}^{2+}$  channel, store-operated  $\text{Ca}^{2+}$  channel and action potential-activated  $\text{Ca}^{2+}$  channel. Note that the peak magnitude of the  $\text{Ca}^{2+}$  movements across the t-tubules are tiny compared with the peak amplitude of the  $\text{Ca}^{2+}$  release flux of SR.





**Figure 2.** Measuring  $\text{Ca}^{2+}$  influx across t-tubules. **A**, a skinned fibre with mag-indo-1 trapped in the t-system and bathed in an internal solution with rhod-2 is excited by a single pulse by field stimulation during confocal line scanning. **B**, confocal line scans of cytoplasmic rhod-2 (**a**) and mag-indo-1 ratio (**R**) in the t-system (**b**). Spatially averaged profiles of the fluorescence signals (**c**) show a net drop in  $\text{Ca}^{2+}$ -dependent t-system fluorescence concurrently with the cytoplasmic  $\text{Ca}^{2+}$  transient, indicating that an inward flux of  $\text{Ca}^{2+}$  across the t-system must have occurred. Modified from Launikonis *et al.* (2009).

muscle work when large amounts of calcium are bound to cytoplasmic  $\text{Ca}^{2+}$  binding sites causing sufficient SR  $\text{Ca}^{2+}$  depletion to activate SOCE.

In skeletal muscle SOCE is activated across the t-system (Fig. 1), providing a proximal source of  $\text{Ca}^{2+}$  for the closely apposed and depleted SR (Launikonis & Ríos, 2007). Thus, extended periods of stimulation can induce a physiologically important entry of  $\text{Ca}^{2+}$  in muscle. However, this still does not provide an explanation for the results of Bianchi & Shanes (1959).

No fast  $\text{Ca}^{2+}$  influx activated by the equivalent of a brief action potential has been reported in adult mammalian skeletal muscle using conventional electrophysiological techniques. Recently, a novel fluorescence technique has allowed the imaging of  $\text{Ca}^{2+}$  transients simultaneously within the lumen of the sealed t-system and open cytoplasmic environment of mechanically skinned fibres from rat (Fig 2). In this preparation the sealed

t-system is able to repolarise in a suitable cytoplasmic environment and develop action potentials when stimulated by a field pulse. An action potential-activated  $\text{Ca}^{2+}$  current (APACC) was observed for the first time using this novel approach, concurrent with the cytoplasmic  $\text{Ca}^{2+}$  transient (Launikonis *et al.* 2009). The physical properties of this current are consistent with an influx of  $\text{Ca}^{2+}$  following each action potential at a sustained low frequency of stimulation or the initial two or three action potentials in a train, with a short rest period in between. APACC has all the major characteristics of the  $\text{Ca}^{2+}$  influx observed by Bianchi & Shanes (1959) and others, strongly suggesting that the excitation-dependent  $\text{Ca}^{2+}$  influx occurring in the adult skeletal muscle is via APACC.

What then, would be the physiological role of APACC? Currently, we can only speculate on this. The small, action potential-dependent  $\text{Ca}^{2+}$  influx may raise the  $[\text{Ca}^{2+}]$  in the vicinity of the ryanodine

receptor before it is first activated by the voltage sensors at the beginning of a tetanus, thus helping the ryanodine receptor to open more fully when it becomes activated. This would also explain the smaller initial force level achieved at the beginning of a tetanus in the absence compared to the presence of extracellular  $\text{Ca}^{2+}$  in the experiments of Lüttgau & Spiecker (1979). The APACC will also cause a transient depletion of  $\text{Ca}^{2+}$  within the transverse tubules. This depletion may activate extracellular  $\text{Ca}^{2+}$  sensors involved in monitoring muscle activity. These and other possibilities remain to be explored. However, it is clear that the excitation-dependent  $\text{Ca}^{2+}$  influx in skeletal muscle has returned to the limelight.

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## Regulation of extracellular pH by purinergic signalling

Little is known about extracellular pH regulation, despite its importance for proper organ functioning. We present data supporting a hypothesis that alkaline phosphatase, through pH-dependent ATP hydrolysis, serves as an extracellular pH sensor. Dysregulation of extracellular pH regulation may help explain the tissue dysfunction characteristic of diseases such as cystic fibrosis

Enzymes function best in a narrow pH range. The pH of the intracellular environment is regulated to within 0.1 pH unit ( $10^{-8}$  M  $[H^+]$ ) by well-described plasma membrane acid–base transporters, although the actual intracellular pH sensor is not known. While many important enzymes have extracellular catalytic sites (ecto-enzymes), less is known about the regulation of extracellular pH ( $pH_o$ ) despite its importance for a variety of cellular processes. Of particular interest is  $pH_o$  regulation in compartments which are thought to have pH far from neutrality, whether acidic in the activated parietal cell canaliculus or osteoclast lacuna, or alkaline at the proximal duodenal surface, the pancreatic duct, salivary gland or the oviduct.

Several ecto-enzymes have strongly acidic and alkaline pH optima, such as the acid and alkaline phosphatases. Although these unusual optima were described decades ago, the physiological significance of such unusual conditions has been largely unknown. Nevertheless, the expression patterns of these enzymes provide valuable clues as to their possible function. For example, acid phosphatases are expressed in the aforementioned acid-secreting organs and also on acidic organelles such as lysosomes, whereas alkaline phosphatase is expressed in the alkali-secreting tissues mentioned above. Importantly, both alkaline phosphatase and acid phosphatase hydrolyse purine nucleotides, in addition to the other organic and inorganic phosphates for which they have hydrolytic activity.

ATP and other purine nucleotides serve as neurotransmitters as part of a purinergic signalling system. Components of the system include exocytotic release of ATP from

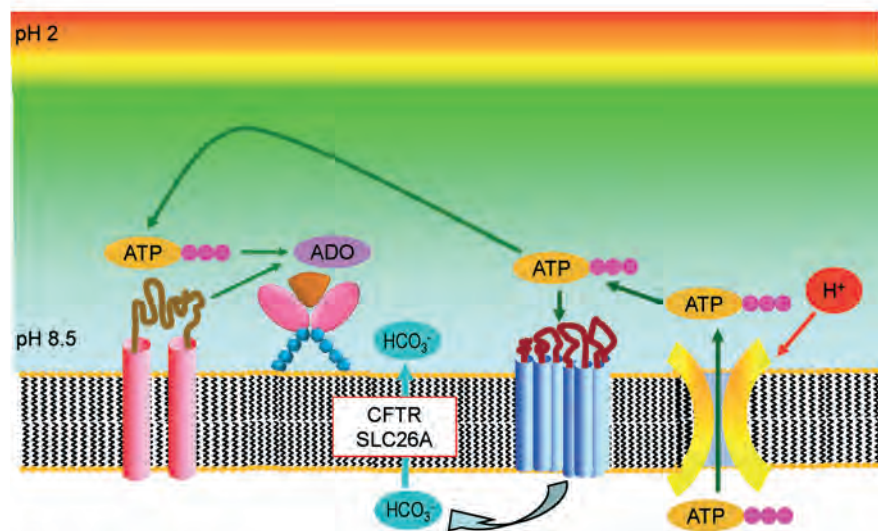


Jonathan Kaunitz and Yasutada Akiba.

subsurface granules, interaction with well-defined purinergic G-protein-coupled cell surface receptors or ionotropic receptors, and hydrolysis by ecto-hydrolases. Although purinergic neurotransmission was initially described in the 1970s, the concept that extracellular ATP is an important non-neuronal regulatory molecule is relatively recent (Leipziger, 2003; Burnstock, 2007). Particularly in secretory epithelia,

extracellular ATP increases anion or  $HCO_3^-$  secretion through interaction with P2Y receptors. Indeed, selective P2Y agonists have been developed to overcome the airway anion secretory impairment characteristic of the disease cystic fibrosis (CF).

Though intuitively wasteful, cellular regulation by extracellular ATP does have the attraction of a signalling molecule present in millimolar concentrations in the cytosol, numerous sensitive and selective cell-surface receptors, and potent ecto-hydrolases such as alkaline phosphatase and ecto-nucleotide phosphohydrolase (ENTPDase or CD39). Nevertheless, the mechanism of epithelial non-lytic ATP release is not well understood, nor is the function of many other membrane proteins and ecto-enzymes that are probably involved.



**Figure 1.** Schematic representation of the duodenal ecto-purinergic  $pH_o$  regulatory system. Bulk luminal  $H^+$  diffuses to the cell surface, where it increases ATP release through a yet uncharacterized non-lytic mechanism. ATP at the cell surface activates membrane P2Y receptors, which in turn raises  $[Ca^{2+}]_i$ , which in turn increases  $HCO_3^-$  secretion to the cell exterior.  $HCO_3^-$  secretion alkalinizes the cell surface, increasing alkaline phosphatase activity, which hydrolyses ATP, decreasing P2Y activation, and diminishing  $HCO_3^-$  secretion. The net effect of this feedback loop is to set cell surface pH at an alkaline value. ADO has a separate signalling system which includes A2 receptors, adenosine deaminase and nucleoside transporters, which are not shown. Abbreviations: ADO, adenosine; CFTR, cystic fibrosis transmembrane regulator; SLC26A, solute cotransporter 26A.

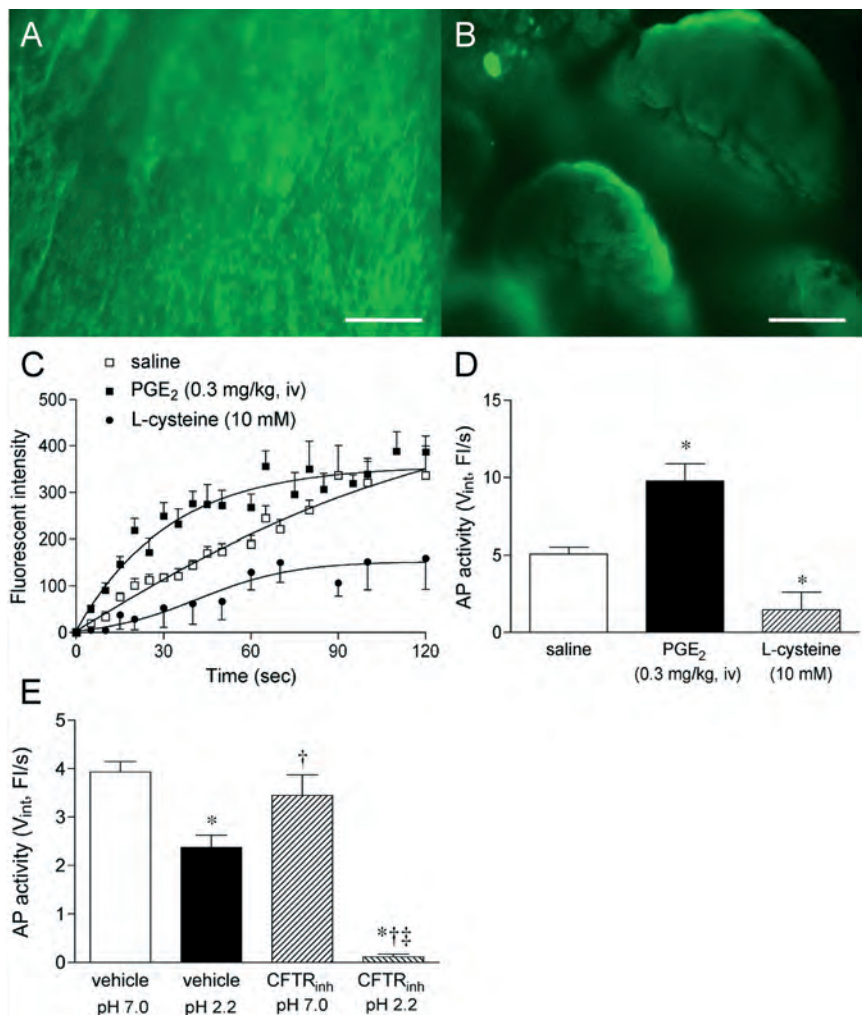


We have recently published data supporting a hypothesis wherein ecto-phosphohydrolases with extreme pH optima serve as  $pH_o$  sensors in alkaline or acidic compartments. We hypothesized that since activation of P2Y receptors increases alkaline secretion into a small compartment, the pH-sensitive hydrolytic activity of alkaline phosphatase (AP) is dependent on local pH, which in turn is set by the rate of alkaline secretion. Thus, for an alkaline compartment, a high rate of alkaline secretion increases the hydrolytic activity of AP, decreasing extracellular ATP concentration ( $[ATP]_o$ ), and decreasing the rate

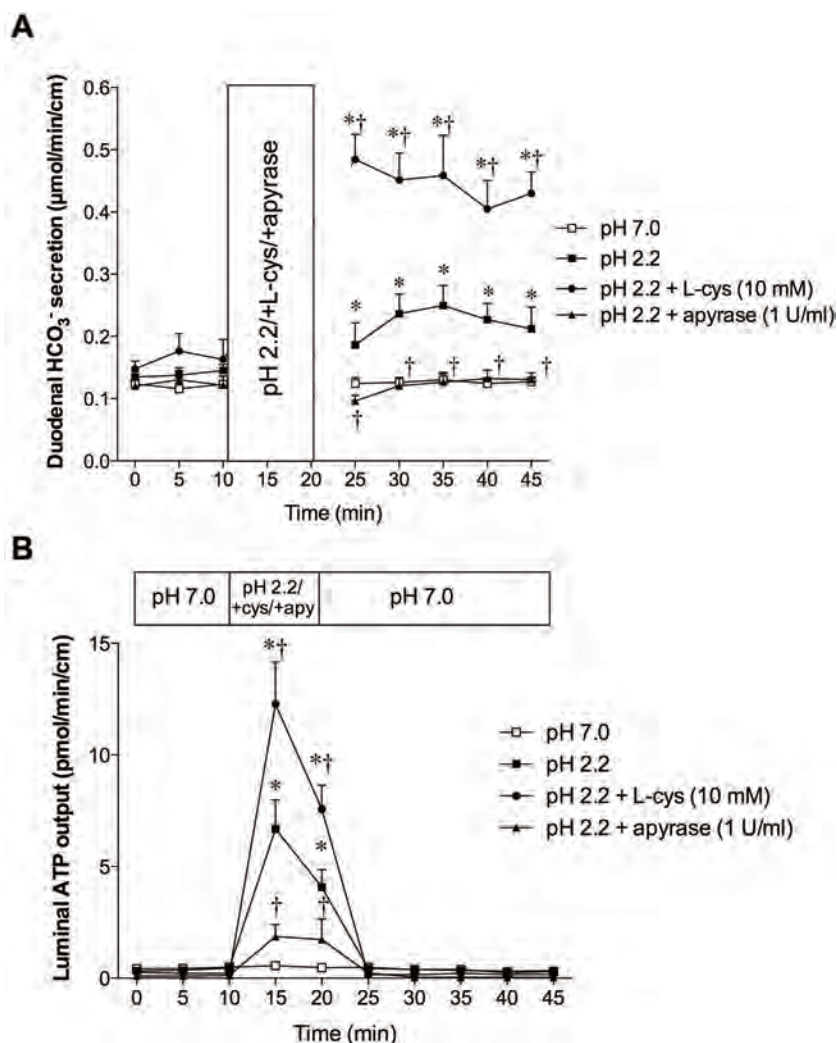
of alkaline secretion, thus serving as a negative feedback loop. In this fashion,  $pH_o$  is regulated by pH-sensitive ATP hydrolytic activity of AP (Fig. 1). To test this hypothesis, we have studied the rat proximal duodenum, the dimensions of which (~5 mm diameter), combined with its accessibility, provide a convenient live-animal system. With this system we have reported that the rat proximal duodenal brush border expresses P2Y<sub>1</sub> receptors, AP and ENTPDase, and that exogenous ATP augments the rate of epithelial  $HCO_3^-$  secretion (Akiba *et al.* 2007; Mizumori *et al.* 2009). One of the cornerstones of the hypothesis is

the presence of pH-dependent AP activity measured *in situ*. Since AP activity had not previously been measured in intact tissues in living animals, we used the fluorogenic AP substrate ELF-97 to measure AP activity *in situ* in living rats (Akiba *et al.* 2007). To vary the  $pH_o$ , we varied perfusate pH or the rate of  $HCO_3^-$  secretion. Perfusion with a pH 2.2 solution, with a > 7 log greater  $[H^+]$  than the AP pH optimum, only decreased AP activity (60% remaining *in situ*) contrasting with the absent activity predicted at pH 2.2 when AP activity is measured *in vitro*. Augmentation of epithelial  $HCO_3^-$  secretion with an I.V. injection of PGE<sub>2</sub> increased the rate of  $HCO_3^-$  secretion, presumably due to elevation of  $pH_o$  (Fig. 2).

The wide availability of potent and selective purinergic agonists and antagonists considerably simplified the biochemical characterization of duodenal ecto-purinergic signalling. Perfusion of the duodenal lumen with an acidic solution, which increases the rate of  $HCO_3^-$  secretion, releases ATP into the lumen at a concentration ~50-fold higher than during perfusion with a neutral solution (Mizumori *et al.* 2009). P2Y<sub>1</sub> antagonists impair the secretory response to exogenous ATP. Importantly, inhibition of AP activity augments  $[ATP]_o$  and increases the rate of  $HCO_3^-$  secretion, supporting ATP hydrolysis as an important component of the mechanism (Fig. 3). Inhibition of the CF transmembrane regulator (CFTR) interestingly impairs ATP release, suggesting a possible mechanism whereby CFTR dysfunction impairs  $HCO_3^-$  secretion. Since an alkaline microclimate overlying the duodenal brush border may protect the underlying mucosa from injury due to gastric acid entering the duodenum, we measured injury of the epithelial cells with the normally excluded DNA-binding dye propidium iodide. A P2Y<sub>1</sub> antagonist markedly increased cellular damage during acid perfusion (Mizumori *et al.* 2009), supporting a protective function of the  $pH_o$  regulatory system.



**Figure 2.** *In vivo* assay of AP activity in rat duodenum. ELF fluorescence *in vivo* in the proximal duodenum was present in the mucus gel layer (A) with little visualization of the underlying epithelial surface. After mucus removal, ELF fluorescence was seen on the surface of villi in rat duodenum (B). Internal bar, 100  $\mu$ m. C, PGE<sub>2</sub> I.V. injection increased the catalytic rate of AP compared with saline control, whereas luminal L-cysteine was inhibitory. D, villous apical surface AP activity was enhanced by PGE<sub>2</sub> I.V. and reduced by L-cysteine co-incubation. E, villous apical surface AP activity was reduced by luminal acidity (pH 2.2), but 60% activity was still present. AP activity measured while perfusion of the pH 2.2 solution disappeared when the animals were pre-treated with a selective CFTR inhibitor CFTRinh-172 (CFTR<sub>inh</sub>, 1 mg kg<sup>-1</sup>, I.P.).



**Figure 3.** HCO<sub>3</sub><sup>-</sup> secretion and ATP release in rat duodenum perfused *in vivo*. A, HCO<sub>3</sub><sup>-</sup> secretion measured by pH stat. Baseline secretion was enhanced by perfusion of luminal acid, consistent with prior reports. The addition of the AP inhibitor L-cysteine further increased HCO<sub>3</sub><sup>-</sup> secretion, whereas the exogenous ATPase apyrase decreased secretion, consistent with AP-mediated ATP hydrolysis and ATP stimulation of HCO<sub>3</sub><sup>-</sup> secretion. B, ATP release, measured by bioluminescence. Luminal acidification increases ATP release, a 50-fold increase. AP inhibition further increases [ATP]<sub>o</sub>, presumably due to inhibition of hydrolysis of ATP by AP. The ATPase apyrase decreased [ATP]<sub>o</sub>.

**Table 1.** Tissues possibly affected by the ecto-purinergic pH<sub>o</sub> regulatory system, on the basis of expression of key components of the system and secretory responses to exogenous ATP. Note that many of these tissues display a phenotype when bearing a CFTR loss-of-function mutation. TNAP, tissue non-specific alkaline phosphatase; TrAP, tartrate-resistant acid phosphatase; PLAP, placental alkaline phosphatase.

Epithelium or tissue	HCO <sub>3</sub> <sup>-</sup> secretion	CFTR expression	AP	ENTPDase	ATP release	P2YR expression	CF phenotype
Airway	+	+	TNAP, PLAP?	+	+	+	+
Bile duct	+	+	TNAP	+	+	+	+
Pancreatic duct	+	+	?	+	+	+	+
Epididymis	+	+	TNAP	?	?	+	+
Oviduct	+	+	PLAP TNAP	?	?	+	+
Duodenum	+	+	IAP	+	+	+	?
Salivary gland	+	+	TNAP	+	+	+	+
Bone	?	+	TNAP (TrAP)	?	?	+	+

The literature abounds with reports of tissues that are likely candidates for ecto-purinergic pH<sub>o</sub> regulation due to expression of several of the required components such as surface P2Y receptors and ecto-ATP-hydrolysing enzymes expression combined with the presence of ecto-nucleotide-provoked HCO<sub>3</sub><sup>-</sup> secretion. Interestingly, many of these tissues also express the CFTR as part of the HCO<sub>3</sub><sup>-</sup> secretory mechanism and are part of the phenotype of CFTR loss of function (Table 1). Thus, it is possible that similar ecto-purinergic regulatory systems control pH<sub>o</sub> in other tissues, where such regulation is important for disparate processes such as sperm capacitation, ciliary beat frequency and bone formation (Kaunitz & Yamaguchi, 2008). We hope that insights derived from further testing of this hypothesis will identify new targets for the treatment of diseases such as CF and other disorders affecting epithelial anion secretion.

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## Fractals in human physiology revisited

Although the idea of applying fractals to cardiovascular signals was first suggested over two decades ago, the actual existence of fractal patterns and their relation to the physiology of cardiac control remains largely unexplored. In this article, we provide a brief overview of the theory behind fractals, and discuss implications for application of fractal statistics to physiological patterns

Across a range of scales, from miles to inches, there can appear a form of self-similarity in structures that is quantifiable by fractal mathematics. It has been suggested that the natural occurrence of fractal structures is manifest in the similarity between the edge of a grain of sand and the edge of a coastline (Mandelbrot, 1982). Self-similarity is not an uncommon form and may have application to physiology. For example, fractal mathematics have been successfully employed to describe the branching patterns in the pulmonary vasculature (Lefèvre, 1983). However, recent advances in computing power and ready access to sophisticated mathematical software has allowed broader usage of fractal statistics to characterize a range of physiological patterns

– including moment-to-moment changes in the heartbeat.

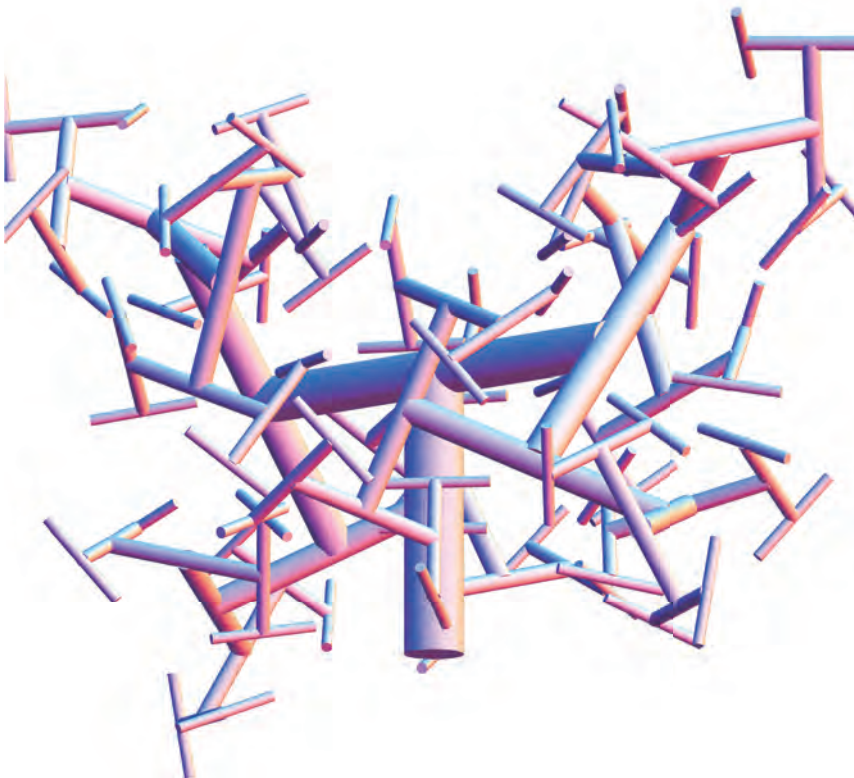
The applicability of fractals to cardiovascular signals was first suggested in the late 80s by Goldberger and colleagues. Since then, it has become popular to assess the fractal nature of beat-to-beat time series of heart period or arterial pressure. However, the idea of a 'fractal' time series is abstract; the fractal character of events that occur at discrete points in time is not readily observable. In contrast, when Mayer performed his experiments in rabbits almost two centuries ago, he observed a clearly distinguishable sinusoidal pattern in arterial pressure and theorized that this pattern relates to the physiological control of the cardiovascular system. As a



Can Ozan Tan (left) and Andrew Taylor.

(perhaps indirect) consequence, the effort to quantify and characterize heart period and arterial pressure variability has been most focused on spectral analysis. However, moving beyond the spectral domain and into the fractal domain may not be warranted. Indeed, as Steven Krantz, in his 1989 critique to Mandelbrot said "the trouble with any subject that relies more on computer output than on theory is that one has to think of something to say about it." (Krantz, 1989)

What does it mean to be fractal? According to the simplest definition, fractal objects are similar at *all* levels of magnification, displaying an inherent property of self-similarity that is infinitely complex (see Fig. 1). Therefore, if heart period is fractal, it must fluctuate with infinitely long as well as infinitesimally small periods, each having a similar pattern. However, by definition, heart beats are discrete events; as such, the resolution of the structure is limited and can be no smaller than the shortest interval between consecutive beats. In fact, partly because the heart beat is discrete, the complexity of the heart period pattern is diminished with each successive magnification (Fig. 2). Nevertheless, if we assume that heart period does display self-similarity and is infinitely complex, what would that mean physiologically? Are fluctuations in the heart beat with a period of 3 s (approximately the length of a



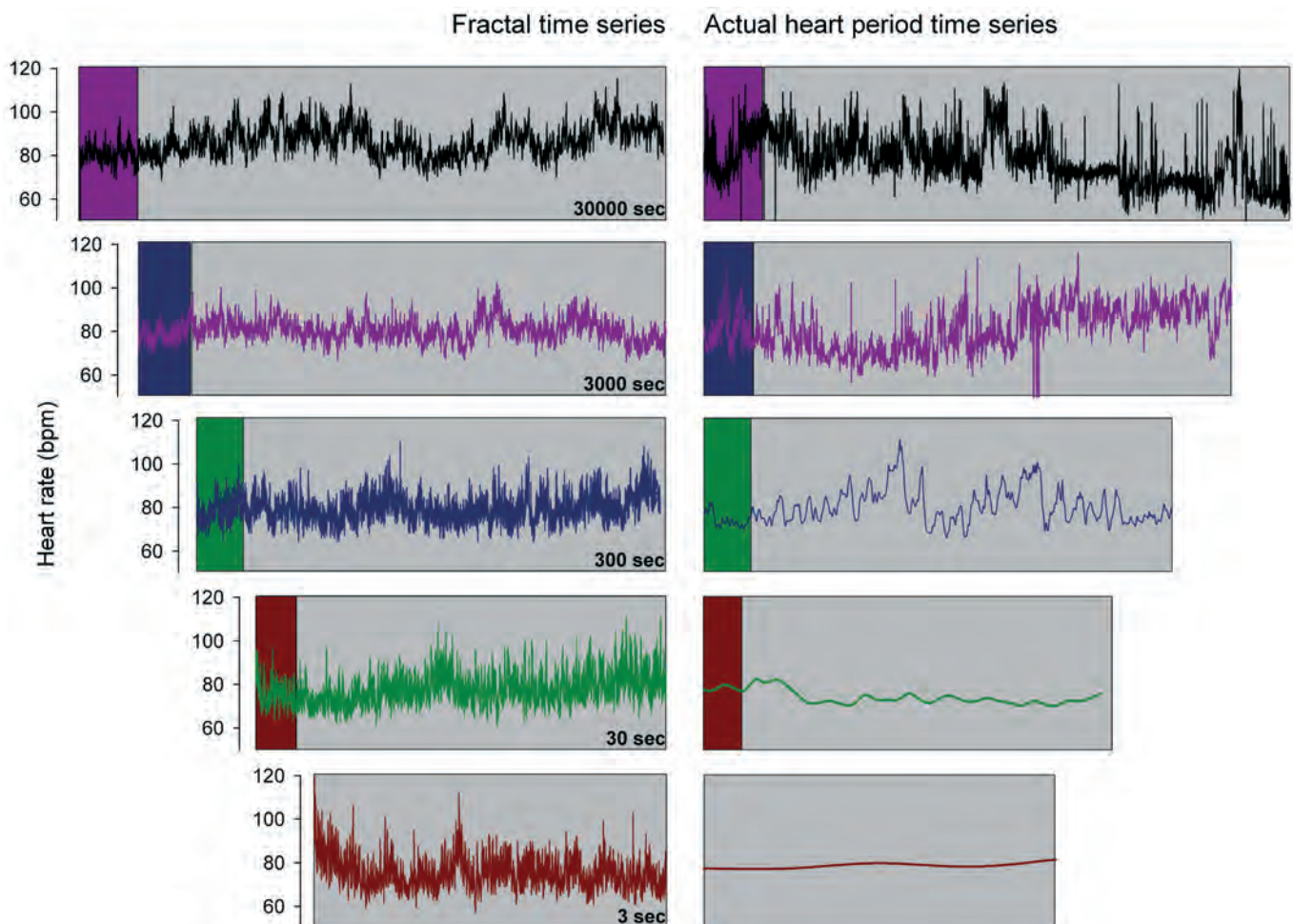
**Figure 1.** An 'H-fractal'. Also called 'Mandelbrot Trees', H-fractals are among the simplest objects that are similar at different levels of magnification (property of self-similarity).

breath) or 33 years (close to half the human life span) both relevant to cardiac autonomic control? Certainly not. Spectral analysis of cardiovascular time series suggests that fast fluctuations in heart rate period (around 6 s and faster) are primarily related to cardiac vagal control, whereas slower fluctuations (around 6–20 s) may reflect both vagal and sympathetic modulation. (It must be noted, though, that the use of spectral analysis to characterize cardiac autonomic control is still under debate; Parati *et al.* 2006; Taylor & Studinger, 2006.) Therefore, fluctuations in heart period, induced by autonomic outflow, appear to have a relatively restricted temporal range. So, could the fractal properties of heart period still provide unique insight to the underlying physiology? One answer was eloquently provided by Francis *et al.* (2002): the fractal scaling

exponent “should not be considered to be a unique cardiovascular indicator in a separate ‘fractal’ class from conventional power-spectral analysis, because it has a clear and comprehensible grounding in spectral analysis.” Thus, the analysis of patterns in cardiovascular time series need not move beyond the spectral domain into the fractal domain.

The application of fractals to heart beat time series assumes that these time series can be defined as fractal processes and that changes in them reflect changes in cardiac control. This assumption arises from anecdotal reports that fractal behaviour could be inferred based on noisy spectrograms and that cardiac disease produced a less noisy spectrogram. However, if the ‘trajectory’ of the heart period time series seems “more like a strange

attractor than like the periodic attractor characteristic of truly regular processes” (Goldberger *et al.* 1990), adequate mathematical testing should be employed to determine the actual presence of the pattern. Instead, power-law ( $1/f$ ) scaling of the power spectral density which can be indicative of a self-similar structure is commonly taken as evidence for fractal behaviour. However, power-law scaling and self-similarity are not sufficient to define truly fractal behaviour (Avnir *et al.* 1998). (A straight Euclidean line is technically self-similar, but obviously not fractal.) Indeed, we have recently shown that despite a strong power-law scaling, a majority of heart period time series in healthy young subjects do not conform to the assumed standard fractal model and therefore cannot be considered fractal processes (Tan *et al.* 2009). If



**Figure 2.** Fractal time series (left panel) and actual heart beats (right panel; data from Stein *et al.* (1999), downloaded from PhysioBank archive) under different levels of magnification (from 500 min to 3 s). Each time series is a magnification of a segment of the plot above (denoted by colour). Fractal time series are generated with the same fractal index as the actual heart beats. In contrast to fractal time series, the complexity of the heart period pattern diminishes with each successive magnification, and almost disappears at time scales (3–30 s) that are most relevant to cardiac autonomic control.



this is true across the range of human health and disease, fractal estimates produce completely meaningless and irreproducible values.

Perhaps because of their unreliability, fractal estimates of heart period variability have no identifiable value that could be considered 'normal'. Fractal estimates can range from 0, reflecting a so-called fractal Gaussian pattern, to 2, reflecting a fractal Brownian pattern. These two are highly distinct; one is stationary and the other is not. Despite the obvious discrepancies in finding both of these patterns, the recent literature reports values as low as 0.7 and as high as 1.2 for healthy young subjects (Struzik *et al.* 2004; Mourot *et al.* 2007). Moreover, very large variability can be observed even under the exact same experimental conditions (Tan *et al.* 2009); estimated fractal indices can range from ~0.5 to ~1.4 for healthy individuals during supine rest (Heffernan *et al.* 2008). To put this range in perspective, these are values that have been reported to represent cardiac control in cyclists during heavy exercise (~0.5; Casties *et al.* 2006) and to reflect the absence of cardiac control in human heart failure (~1.3; Goldberger *et al.* 2002).

Lastly, it might be worthwhile to consider the *raison d'être* for potential fractal behaviour in heart period variability. It has been theorized that the absence of a characteristic time scale (*a la* fractal fluctuations) facilitates the functional adaptive capacity of the cardiovascular system by helping to prevent 'excessive mode locking.' This would be along the lines of pervasive oscillations present in some pathological conditions, such as in heart failure (Peng *et al.* 1993). Improved adaptive capacity via fractal patterns is, in fact, a plausible theory, and could well be true. However, the presence of random noise (which abounds in biological systems) can serve exactly the same purpose; the contribution of a fractal, scale-independent mechanism is not crucial. Therefore, it is incumbent upon the theorizer to

unambiguously define the presence of a fractal pattern *versus* simple random noise.

More than two decades ago, when it was first proposed that the heart period is fractal, it was suggested that physiology may prove to be a rich source for the study of fractals as well as other types of non-linear dynamics (Goldberger *et al.* 1990). However, exploration of fractals should avoid being self-referential, generating "pictures to learn more about the pictures" (Krantz, 1989). Although application of sophisticated analyses to cardiovascular data can lead to deeper understanding, it also has the potential to cloud our view of the physiology.

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## Sheet-like tendons are stiffened by bulging muscles

The common shape changes of a contracting muscle can load aponeuroses along multiple axes. The close interaction of these sheet-like tendons with the muscle belly dynamically modulates stiffness and allows aponeuroses to function as variable stiffness springs

The forces generated by the contractile machinery of skeletal muscle are transmitted to the skeleton through tendons. Most tendons don't simply transmit forces but rather behave like springs, stretching as muscular forces are applied and recoiling as forces decline. The significance of tendon elasticity is most obvious in cyclical movements where elastic energy can be stored and recovered with tremendous efficiency thereby lowering the energetic cost of movement. An extreme example of this mechanism is the bouncy gaits of hopping wallabies, where it has been shown that tendon stretch and recoil can allow the organism to recycle nearly all of the energy from a previous stride (Biewener & Baudinette, 1995). This elastic behaviour of tendons extends well beyond such obviously bouncy gaits and also increases the energetic economy of walking and running.

As a biological spring, the capacity of a tendon for storing elastic energy is largely determined by its stiffness. The mechanical energy stored in tendons is a function of the force applied to the tendon and length changes the tendon undergoes in response to that load. This relationship simplifies biomechanical models, where energy storage can be calculated from the modelled muscle force and a tendon's characteristic stiffness (Zajac, 1989). This approach assumes that a given tendon is governed by a single relationship between force and length that defines a single stiffness. *In situ* measurements of isolated tendons suggest that this assumption is valid for so-called 'free' tendons, such as the Achilles, that span a gap between muscle and bone (Fig. 1).

However, free tendons are not the only elastic structures capable of storing elastic energy. In many muscles the free tendon is continuous with broad sheet-like tendons, or aponeuroses, that function as the attachment and insertion sites for muscle fibres (Fig. 1). Both tendons and aponeuroses consist of collagen bundles oriented primarily along the

muscle's line of action embedded in an extra-cellular matrix. In fact, the same collagen bundle may extend from the tendon to the aponeurosis with no structural separation. These shared structural features have been used to infer functional similarity between tendons and aponeuroses. It is commonly assumed that the stiffness of an aponeurosis is the same as that of the free tendon, though some recent measurements challenge this assumption (e.g. Magnusson *et al.* 2003).

Although aponeuroses share some structural similarities with free tendons, they probably undergo a more complex loading regime. Many aponeuroses cover a substantial



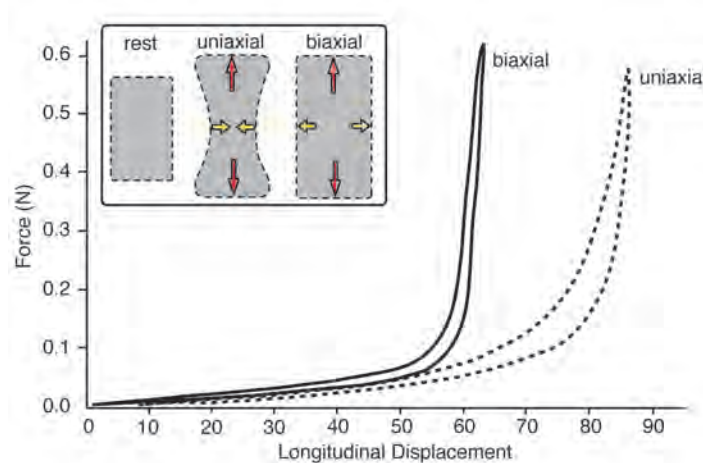
**Figure 1.** Superficial view of the lower leg highlighting the Achilles tendon and the aponeuroses of the gastrocnemius muscles.



Manny Azizi (left) and Thomas Roberts.

portion of the muscle belly (Fig. 1). It is well accepted that when muscles contract and fibres shorten, the muscle expands in other dimensions to maintain a constant volume. The image of a flexing bodybuilder is a familiar reminder that muscles change shape when they contract. Given the close association of aponeuroses with the muscle belly, it is reasonable to predict that shape changes in a contracting muscle may also deform the aponeurosis along multiple axes.

In a recent paper we used high-speed fluoroscopy to characterize three-dimensional deformations in aponeuroses during muscle contraction (Azizi & Roberts, 2009). Our measurements confirmed that aponeuroses are stretched both parallel and perpendicular to a muscle's line of action during muscle contraction. This pattern of stretch indicates that the aponeurosis is loaded biaxially.



**Figure 2.** The effect of biaxial loading on stiffness. Inset, a schematic showing the deformations that occur in a hypothetical tissue during uniaxial and biaxial loading. Force-deformation curves for a tissue loaded uniaxially and biaxially. The slopes of these curves characterize tissue stiffness. The curves highlight the increased force required to stretch a tissue by a given amount during biaxial loading. Curves are modified from Lanir & Fung, 1974.

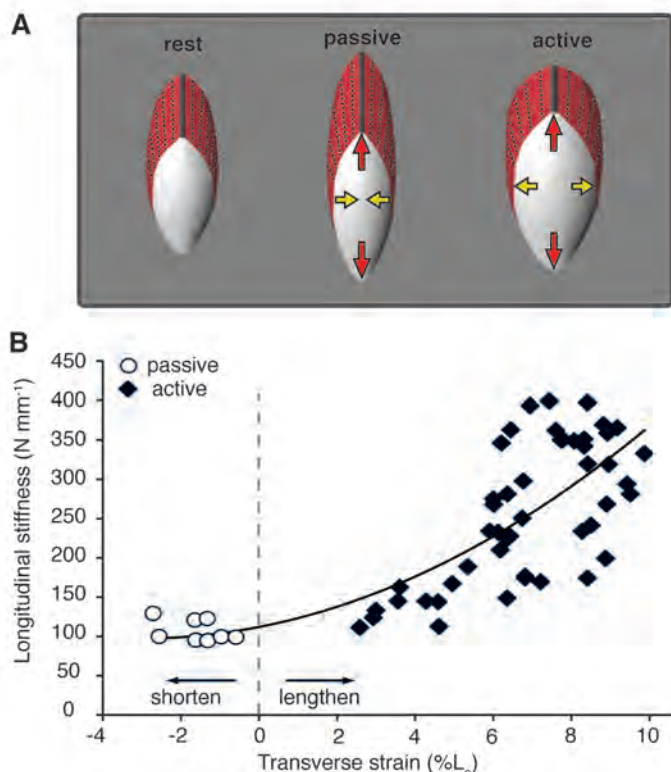


To appreciate the functional significance of biaxial loading, consider a case where the tissue is only loaded in one direction. When loaded uniaxially any solid material will tend to get thinner in directions perpendicular to the line of pull; a stretched rubber band displays a characteristic 'necking' where it shortens perpendicular to the direction of loading (Fig. 2). In contrast, under biaxial loading the tissue is prevented from shortening, and with enough loading can be stretched in two dimensions. Biaxial loading requires more force for a given stretch (Fig. 2). What this means for muscle is that the effective stiffness of the tendon spring is greater in the longitudinal direction than would be expected for uniaxial loading (Fig. 2).

We were able to test the idea that biaxial loading increases the effective stiffness of aponeurosis by comparing the aponeurosis stiffness during active and passive force production. When the muscle was loaded passively (by stretching it to long lengths), the aponeurosis shortened in the

orthogonal direction, as expected for uniaxial loading (Fig. 3). The stiffness measured under these conditions was significantly lower than the stiffness measured for biaxial loading during active force production (Fig. 3).

The effects of biaxial loading may explain previously published results that were considered difficult to reconcile with a model of the aponeurosis as a uniaxially loaded spring. Measurements on isolated muscles found the stiffness of the aponeurosis along the muscle's line of action increases substantially in active as compared with passive force production (Zuurbier *et al.* 1994; Lieber *et al.* 2000). Such changes in aponeurosis stiffness were difficult to explain when only deformations along the muscle's line of action were considered. However, when one considers the length changes that occur orthogonal to the muscle's line of action, it becomes clear that biaxial loading provides a likely mechanism for stiffness modulation in aponeuroses (Fig. 3).



**Figure 3.** The behaviour of aponeuroses during passive and active force production. A, a schematic of a muscle showing the deformations that occur in the aponeurosis during passive and active force production (muscle in red, aponeurosis in white). Length changes along the muscle's line of action (longitudinal) are indicated by red arrows and length changes perpendicular to the muscle's line of action (transverse) are indicated by yellow arrows. B, data showing that relative length changes perpendicular to the line of action (transverse strain) can modulate the stiffness of the aponeurosis along the muscle's line action (longitudinal stiffness).

Variable stiffness in aponeuroses may have important implications for movement. The use of stiffness values based on uniaxial material properties may underestimate the elastic energy stored in aponeuroses during active contractions. Variable stiffness may also have implications for motor control. If the muscle 'sees' a different spring stiffness under different conditions, the motor control system must accommodate this variability. The degree to which changes in aponeurosis stiffness are tuned to the mechanical demands of movement remain unknown and should provide fertile ground for future studies.

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## The placebo response: how words and rituals change brain circuitry

The study of the placebo response is basically the study of the effects of the psychosocial context and the ritual of the therapeutic act on the patient's brain. Recent research in Parkinsonian patients indicates that the therapist's words and rituals may induce molecular and cellular changes in the patient's brain, thus placing the doctor-patient relationship and psychotherapy into the neurobiological domain

The placebo response, or placebo effect, is the therapeutic effect that follows the administration of an inert treatment (the placebo), for example, a saline solution or a sugar pill. Neither salt nor sugar will ever acquire therapeutic properties. What matters is the psychosocial context around the treatment. In fact, a patient who receives a therapy is deluged with social and sensory stimuli which tell him that a therapy is being performed. This induces expectations of clinical improvement and may affect several systems and apparatuses, producing a real benefit. Therefore, the study of the placebo response is the study of how the patient's brain is affected by the psychosocial context around the treatment.

### Placebos induce dopamine release in Parkinsonian patients

Many medical conditions are affected by placebo administration. Typically, when one administers a placebo, the patient is given a fake treatment along with verbal suggestions of benefit. Overall, the whole ritual of therapy administration constitutes the therapeutic act. There is now compelling experimental evidence that the therapeutic act, together with the doctor's words and rituals (crucial elements of a placebo procedure), may induce changes in the patient's brain, such as the release of endogenous opioids and the activation of different brain regions in subjects who are in pain. Likewise, placebos may activate different regions in depressed patients, and may also induce the release of immune mediators and hormones (Benedetti, 2008; Zubieta & Stohler, 2009).

One of the most interesting models and medical conditions that has been investigated to understand the



From top left clockwise: Fabrizio Benedetti, Michele Lanotte and Leonardo Lopiano.

neurobiological underpinnings of the placebo response is Parkinson's disease, a motor disorder that is highly responsive to placebo treatments. In 2001, de la Fuente-Fernandez *et al.* (2001) conducted the first brain imaging study of the placebo effect by means of positron emission tomography. These researchers assessed the release of endogenous dopamine by using raclopride, a radiotracer which binds to dopamine D2 and D3 receptors and competes with endogenous dopamine. In this study, patients were aware that they would be receiving an injection of either active drug (apomorphine, a dopamine receptor agonist) or placebo, according to classical clinical trial methodology. After placebo administration, it was found that dopamine was released in the striatum, corresponding to a change of 200% or more in extracellular dopamine concentration and comparable to the response to amphetamine in subjects with an intact dopamine system. The release of dopamine in the motor striatum (putamen and dorsal caudate) was greater in those patients who reported clinical improvement.

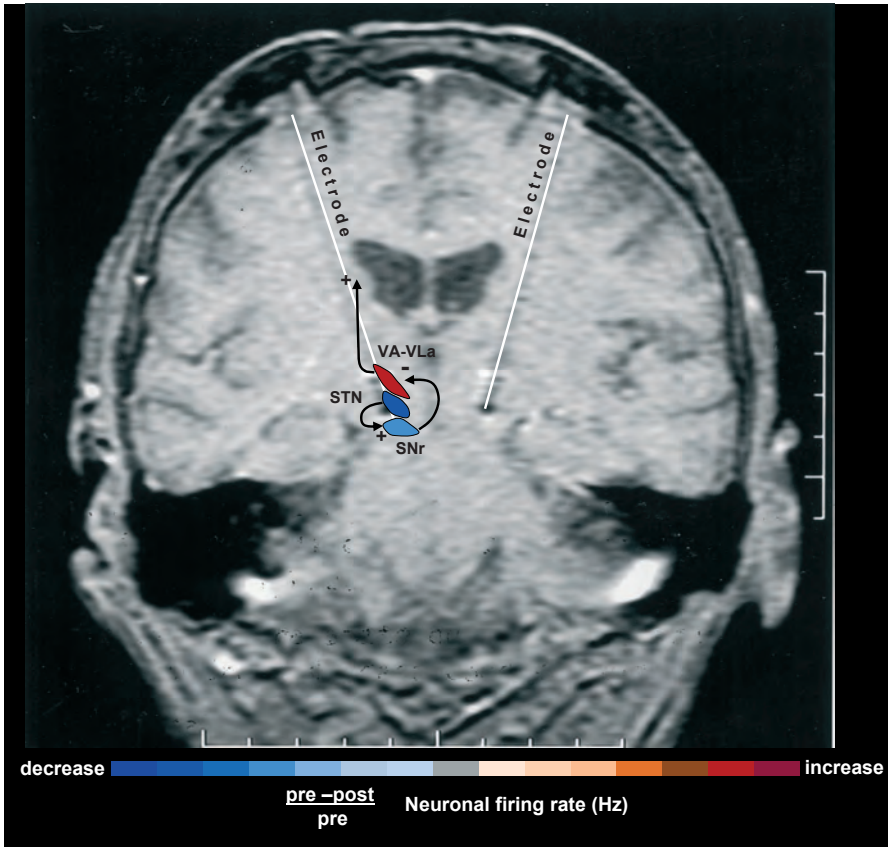
Although in the studies by de la Fuente-Fernandez *et al.* (2001) all patients showed dopamine placebo responses, only half of the patients

reported motor improvement. These patients also released larger amounts of dopamine in the dorsal motor striatum, suggesting a relationship between the amount of dorsal striatal dopamine release and clinical benefit. This relationship was not present in the ventral striatum, in which all patients showed increased dopamine release, irrespective of whether they perceived any improvement. Compared to the dorsal motor striatum, the ventral striatum (nucleus accumbens) is involved in motivation and reward anticipation. Accordingly, the investigators proposed that the dopamine released in the ventral striatum was associated with the patients' expectation of improvement in their symptoms, which could in turn be considered a form of reward.

### A placebo treatment changes neuronal activity in the basal ganglia

In 2004, the first study of the placebo effect at the single-neuron level was performed (Benedetti *et al.* 2004). Since the subthalamic nucleus plays an essential role in basal ganglia functioning and is a major target in the surgical therapy of Parkinson's disease, we performed a double-blind study in which the activity from single neurons in the subthalamic nucleus before and after placebo administration was recorded to see whether neuronal changes were associated to the clinical placebo response. Before placebo administration, the activity of neurons was recorded from one subthalamic nucleus prior to implantation of the first electrode and used as a control. After the placebo, which consisted of a subcutaneous injection of saline solution along with the verbal suggestion of motor improvement,

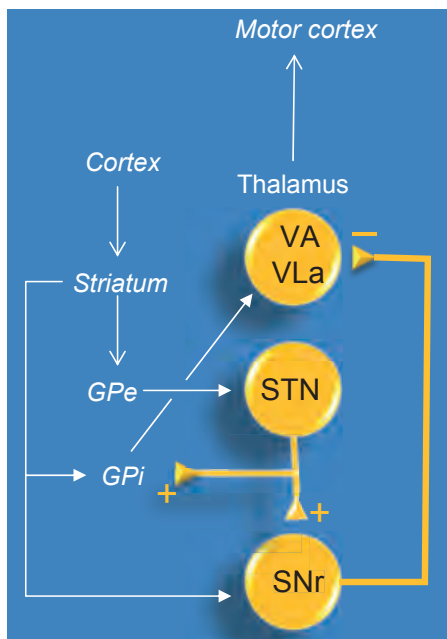




**Figure 1.** Neuronal changes during a placebo treatment in a Parkinsonian patient. Whereas there is a decrease in firing rate in the subthalamic nucleus (STN) and substantia nigra pars reticulata (SNr), an increase occurs in the ventral anterior (VA) and anterior ventral lateral (VLa) thalamus. The colour scale indicates the changes in firing rate compared with baseline. The black arrows indicate the excitatory (+) and inhibitory (–) connections between these regions.

neuronal activity was recorded from neurons prior to implantation of the second electrode into the other subthalamic nucleus. Those patients who showed a straightforward clinical placebo response, assessed

by means of arm rigidity and subjective report of well-being, also showed a significant decrease of firing rate and a shift from bursting to non-bursting activity compared to the pre-placebo subthalamic



**Figure 2.** The neuronal circuit that is affected by a placebo treatment in Parkinson's disease is shown in yellow. It is probably only a part of a more complex circuit, which is shown in white. The subthalamic nucleus (STN) neurons, which receive inputs from the cortex, the striatum, the external globus pallidus (GPe) as well as from other regions, send their output excitatory information to different regions, such as the substantia nigra pars reticulata (SNr) and the internal globus pallidus (GPi). SNr has an inhibitory connection with the thalamus, and the thalamus sends projections to the motor cortex. The striatum also sends projections to GPi, which in turn projects to the thalamus, and to SNr.

nucleus. In order to rule out the possibility that the difference in firing rate between the pre- and post-placebo subthalamic nucleus was independent of the placebo treatment itself, a no-treatment group (natural history) was studied. The patients of this no-treatment group did not undergo any placebo treatment between the implantation of the first and second electrode. All these patients showed no significant differences between the neuronal firing rates of the two subthalamic nuclei, which indicates that the difference between the first and the second side of implantation in the placebo group was due to the placebo intervention *per se*.

In a more recent study, these findings were extended from the subthalamic nucleus to other nuclei, thereby characterizing a complex neuronal circuit during the placebo response (Benedetti *et al.* 2009). In those patients who showed a clinical placebo response, there was a decrease in firing rate in subthalamic nucleus neurons that was associated with a decrease in the substantia nigra pars reticulata and an increase in the ventral anterior and anterior ventral lateral thalamus (Fig. 1). By contrast, placebo non-responders showed either a lack of changes in this circuit or partial changes in the subthalamic nucleus only. Thus, changes in activity in the whole basal ganglia–thalamic circuit appear to be important in order to observe a clinical placebo improvement. These findings indicate that a placebo treatment, which is basically characterized by verbal suggestions of benefit, can reverse the malfunction of a complex neuronal circuit, although these placebo-associated neuronal changes are short-lasting and occur only in some patients but not in others.

The circuit we have characterized (Benedetti *et al.* 2009) is likely to be a part of a more complex circuitry, including the striatum and the internal globus pallidus (GPi), that is modified by placebo administration (Fig. 2). These placebo-induced changes may have

profound implications for both the doctor–patient relationship and psychotherapy. In fact, the psychosocial context and the therapeutic act itself, along with verbally induced expectations of clinical benefit, may indeed induce specific changes in the patient's brain, thus placing the therapist–patient communication and psychotherapy into a therapeutic context which *per se* is capable of modifying the patient's brain.

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#### Swartz Prize

Horace Barlow from the Cambridge Physiological Laboratory has recently won the Swartz Prize for Theoretical and Computational Neuroscience. The Prize is awarded annually to:

an individual whose activities over a period of time have produced a significant cumulative contribution to theoretical models or computational methods in neuroscience, or to:

a person who has made a particularly noteworthy advance over the past several years in theoretical or computational neuroscience.

## Neuromuscular interaction during human walking: how do changes in muscle–tendon mechanics affect the motor control of walking?

Prolonged walking can increase the compliance of soleus tendinous tissues, which could ultimately impair the ability to recover from a sudden balance disturbance

When humans walk, muscle–tendon units in the legs are constantly subjected to length changes, which are distributed between the muscle and tendinous tissues within the muscle–tendon unit. These length changes can affect the activity of afferent receptors located in the muscle. One situation where this is particularly important is when encountering an unexpected balance disturbance during walking, such as a trip or stumble. In order to avoid falling, the central nervous system must be able to detect the disturbance and initiate a response, all in a matter of milliseconds.

### Investigating neural and mechanical behaviour simultaneously

A wealth of data have been presented investigating sensory feedback in humans during walking, and this has without question improved our understanding of human motor control. However, since many of the receptors that contribute to afferent feedback during walking are located in the muscle and tendinous tissues, it has become increasingly desirable to investigate the behaviour of these tissues, and to relate it to sensory feedback. One method that has facilitated experiments in this field is ultrasonography. Although this method is traditionally associated with fetal scanning, the last two decades have seen an adaptation to the methodology that has allowed the study of muscle and tendon length changes during dynamic movements. Although the method is naturally limited by the fact that it is 2-dimensional, it has nonetheless provided valuable information about muscle and tendon mechanics during movement.



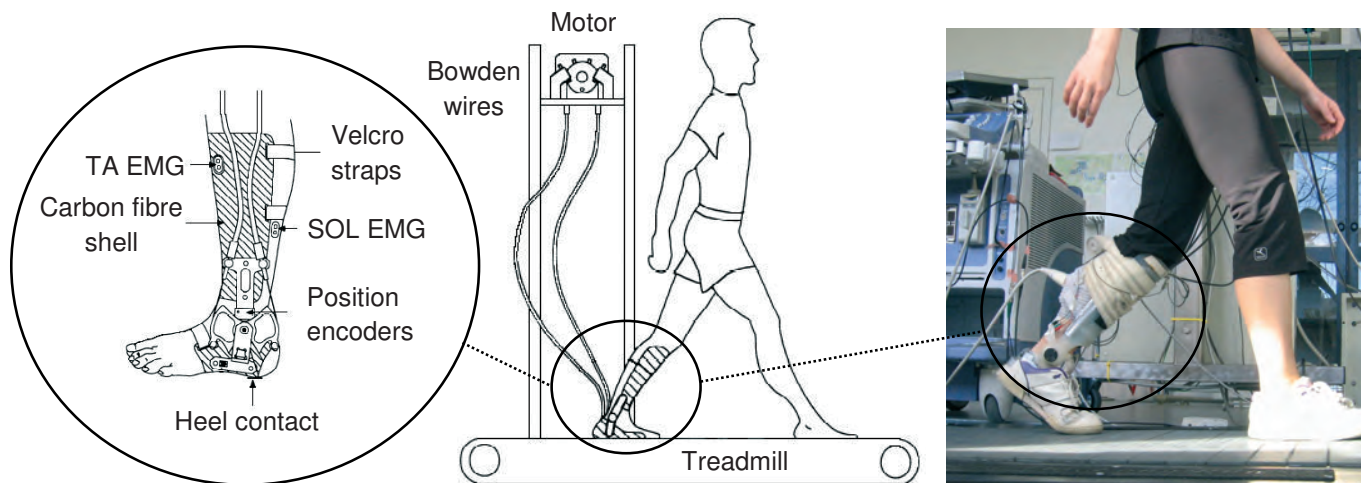
Neil Cronin.

### Neuromuscular interaction during walking: what happens when we walk for a long time?

It has previously been shown that after a 1 h period of repeated passive stretching of the human ankle extensor muscles, the compliance of the tendinous tissues (outer tendon and aponeuroses) increases (Avela *et al.* 2004). If the same phenomenon were present during walking, increased tendinous tissue compliance could affect the firing behaviour of sensory receptors within the muscle–tendon unit, such as the muscle spindles. These receptors are thought to make an important contribution to muscle activation during normal walking, as well as in response to an unexpected balance disturbance (Sinkjaer *et al.* 2000). Therefore, changes in tendinous tissue compliance could affect the motor control of human walking.

We recently sought to examine whether changes in tendinous tissue compliance were indeed evident during human walking in a group of 11 young, healthy adults (Cronin *et al.* 2009). Subjects walked on a treadmill for 75 min with a portable robotic actuator attached to the ankle joint. This device is capable of eliciting rapid ankle dorsiflexion perturbations during the stance phase of walking (Fig. 1). Full details of the device are presented





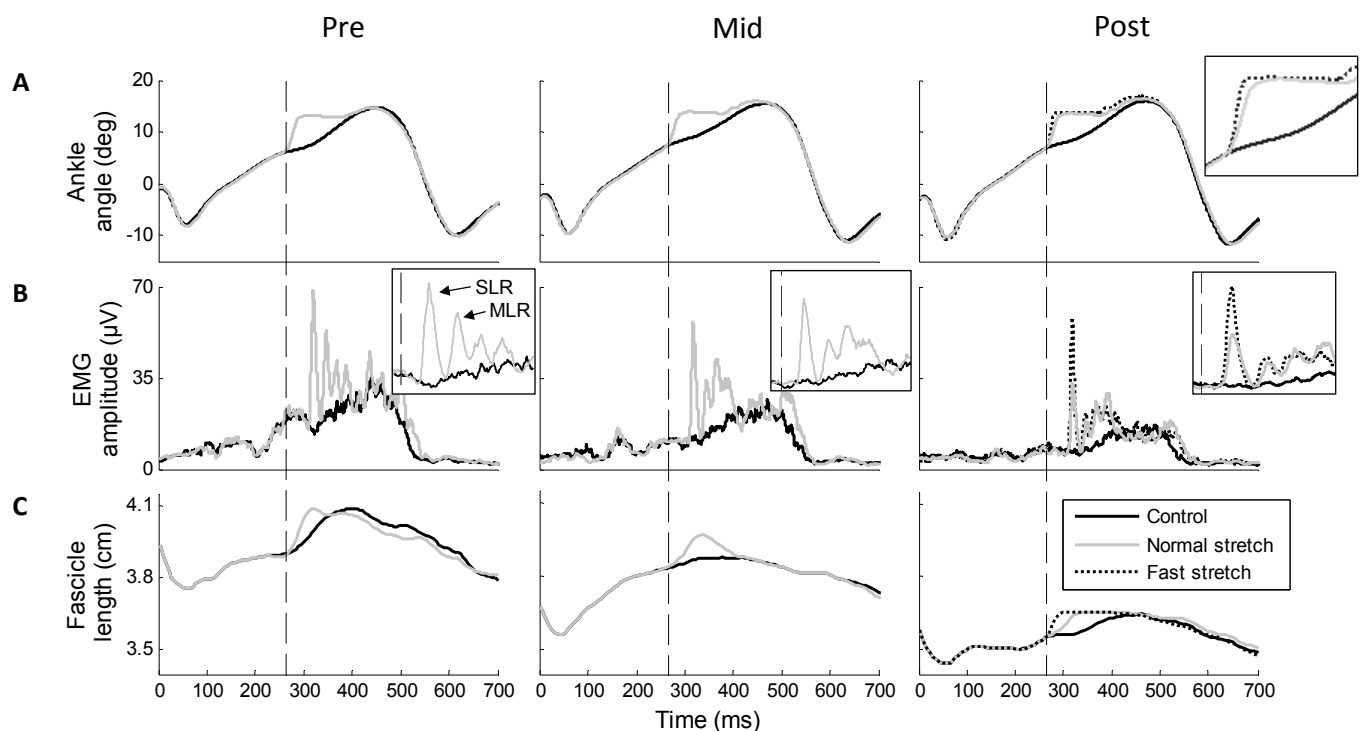
**Figure 1.** Schematic of the robotic actuator that was used to elicit rapid dorsiflexion perturbations during walking. This device was combined with surface EMG and ultrasonography. A fully instrumented subject is shown in the right panel.

elsewhere (Andersen & Sinkjaer, 2003). By combining this method with ultrasonography and surface electromyography (EMG), it was possible to examine changes in both muscle fascicle length and muscle activation in the soleus muscle throughout an exercise protocol.

Rapid stretches were imposed at the ankle joint at three time intervals representing the early,

mid and late phases of the 75 min walking protocol (Pre, Mid and Post, respectively). Between the Pre and Post intervals, the amplitude and velocity of fascicle stretch both decreased considerably (by 46% and 59%, respectively; mean values across all subjects), as did short and medium latency stretch reflex amplitudes (by 33 and 25%, respectively) in response to a constant external perturbation.

Furthermore, in response to a faster perturbation elicited at the Post interval, the amplitude of the short latency component and the velocity of muscle fascicle stretch both recovered to pre-exercise values (Fig. 2). These findings clearly show that when perturbations were elicited at the Post interval, the stretch was not transmitted as effectively to the muscle fascicles, and thus to the muscle spindles.



**Figure 2.** Neural and mechanical stretch responses from one representative subject at the Pre, Mid and Post intervals. A, mean ankle trajectory ( $n = 28$ ); B, SOL EMG activity ( $n = 28$ ); C, fascicle length ( $n = 3$ ). Dashed vertical lines represent the onset of the rapid perturbations. The enlarged insets are not shown to scale, but are intended to highlight the individual traces more clearly. SLR and MLR, short and medium latency stretch reflex, respectively.

This would explain why short and medium latency stretch reflex amplitudes decreased, as they are at least partly mediated by type Ia and type II afferents, respectively, both of which originate in the muscle spindles. At the Post interval, we also observed a decrease in fascicle length at the point of ground contact and immediately prior to the onset of the perturbation, as well as a smaller fascicle length change throughout the stance phase. Concurrently, the range of joint motion at the ankle during walking was unchanged throughout the study. Taken together, these findings provided strong evidence for an increase in the compliance of tendinous tissues after walking in the human soleus muscle–tendon unit.

Interestingly, during normal unperturbed walking, a general decrease in ongoing soleus muscle activity was observed ('Control' traces in Fig. 2). This may be an indication that the increased tendinous tissue compliance led to a decrease in the ongoing sensory feedback from muscle receptors, which is known to contribute to muscle activity during unrestrained walking (Sinkjaer *et al.* 2000). As with the responses to perturbations, this is probably due to the fact that the stretch stimulus reaching the muscle fascicles (and receptors) decreased after the walking protocol.

### What are the functional implications?

Based on data obtained with ultrasonography, it is known that when a muscle–tendon unit changes length, the actual length changes of the muscle and tendon components may be uncoupled (e.g. Ishikawa *et al.* 2005). In this context, the increase in tendinous tissue compliance that we have observed could enable the muscle fibres to contract relatively slowly (Lichtwark & Wilson, 2008), whilst the larger tendinous tissue stretch during the stance phase would facilitate the storage of elastic energy in the tendinous tissues. This could potentially increase the efficiency of the soleus muscle–tendon unit.

However, this raises an interesting series of questions. What happens in the other muscle–tendon units of the lower limb? If muscle activation decreases in soleus, how does the central nervous system compensate in order to maintain the same movement pattern? Furthermore, if the amplitude of stretch reflexes decrease after a sustained period of walking, and these responses are important for recovery from unexpected balance disturbances (Sinkjaer *et al.* 2000), are the responses to such disturbances compromised after prolonged walking? As the soleus muscle is just one of the plantarflexors, it is possible that activation of other synergistic muscles increases in response to decreased soleus activation. Indeed, this kind of neural compensation has been reported after higher intensity fatiguing exercise (Akima *et al.* 2002). This is a matter of ongoing study in our laboratory, and the results will help us to understand how the central nervous system adapts to time-dependent changes in muscle–tendon mechanics.

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## Brown coats or white?

In Edinburgh in the late 1940s students wore white (or, more accurately 'off-white') lab coats for practical classes as did most of the technicians. Mr Marshall, the histology wizard, chose grey but I didn't encounter many brown coats till I arrived at the (then) Institute of Animal Physiology at Babraham. Here they were worn by animal house and workshop staff, and by the indispensable heavy-duty handy men – occasionally termed 'heavy-handed duty men' from their propensity to slosh distilled water about the lab while delivering it in winchesters from the central still.

Babraham's first Director Ivan de Burgh Daly favoured white coats for himself and the rest of the scientific staff, despite having worked with W. M. Bayliss. In his Bayliss–Starling Memorial Lecture, Daly said that Bayliss '*always wore his brown overall, which had seen better days, in the laboratory, and as long as I knew him it did not seem to change. I imagine therefore that the memo to be found in one of his notebooks which runs "Overalls, 35 inches, price 4s. 3d. [21p] post free" supplied by a firm in Newcastle, was a reminder in the event of an emergency which never emerged*'.

I de Burgh Daly (1967) The Bayliss–Starling Memorial Lecture. *J Physiol* **191**, 1–23.



## Multiple tests correction, false discovery rate and $q$ value

In the second of the microarray data analysis articles of this *Techniques* series Fumiaki Katagiri (below) from the University of Minnesota, USA, examines the false discovery rate in more detail and reveals why this method is more suitably adapted to multidimensional data, such as that generated by microarrays

Major statistical challenges for analysis of a very large context dependent data set generated by a highly parallel method, such as a microarray data set, are two-fold: a small number of replicates due to the high cost of data generation, and the need for a very large number of significance tests. The purpose of this article is to discuss the latter, the problem of multiple testing.

### What is multiple tests correction?

Let's assume that we measured expression level values of 10 000 genes in two tissues, kidney and liver, from each of five individual mice (five biological replicates). We have already applied a transformation, such as  $\log_2$ -transformation, to the expression level values to make the sample distributions approximately normal. We ran a significance test, such as a  $t$  test, for each gene to calculate the  $P$  value for the hypothesis that the expression levels in the two tissues are the same (null hypothesis). So, the smaller the  $P$  value is, the more likely it is that the gene is differentially expressed. First, assume that no gene is differentially expressed in two tissues, i.e. all the genes are nulls. Figure 1A shows the distribution of simulated  $P$  values of the 10 000 genes in a histogram with an interval of  $P = 0.01$  each, when all the genes are null. Yes, it is a uniform distribution – with this interval size, each band height is on average  $10\,000 \times 0.01 = 100$  genes (red line). We will use this uniform distribution with 100 genes per interval as the null distribution estimate. If we use the significance level (i.e. the threshold  $P$  value) of 0.05 to select positive genes, approximately 500 genes (left of the blue line) are selected with the null distribution. Since all the genes are null, these 500 genes are all false positives (type I errors). Thus,



using a significance level commonly used when the number of tests is small results in many false positives when the number of tests is large. We should use a lower significance level to avoid a high number of false positives, but how can we determine an appropriate significance level? Methods to correct the significance level are called multiple tests corrections (or multiple comparisons corrections).

### A classical type of multiple tests correction

The Bonferroni correction is a classical correction method. According to the Bonferroni correction, the significance level to be used for each of 10 000 tests is  $0.05/10\,000 = 5 \times 10^{-6}$ . Using this method, it is very unlikely that any false positives will be selected in the all-null situation in Fig. 1A. The Bonferroni correction makes the probability of selecting one or more false positives equal to 0.05. Unfortunately, a fundamental principle of statistical analysis is that fewer false positives are associated with more false negatives (type II errors), that is, a higher chance of missing truly differentially expressed genes. Let us assume that we had some genes with a mean expression level difference of 2.5 between kidney and liver in mice and that the expression level in each tissue has a standard deviation of 1 (if we

could measure the expression level values from a very large number of mice). As shown in Fig. 2, the distributions of expression levels in kidney and liver would be quite well separated. We can calculate what power we would get for this kind of truly differentially expressed genes using 5 replicates and a significance level of  $5 \times 10^{-6}$  according to the Bonferroni correction. The power in this case is 0.006, i.e. if we have 500 such truly differentially expressed genes among 10 000 genes, then on average we would only identify three genes as being differentially expressed. We would miss the vast majority of them! For most research questions, this is not an acceptable level of power. So, the Bonferroni correction is too stringent. How can we get a good balance between the numbers of false positives and false negatives?

There are several multiple tests correction methods of the classical type that are more relaxed than the Bonferroni correction. However, one common problem associated with the classical type of multiple tests correction is that when the number of positives is relatively close to the expected number for false positives, we cannot estimate how many of the positives could be true positives.

### False discovery rate (FDR), a new type of multiple tests correction

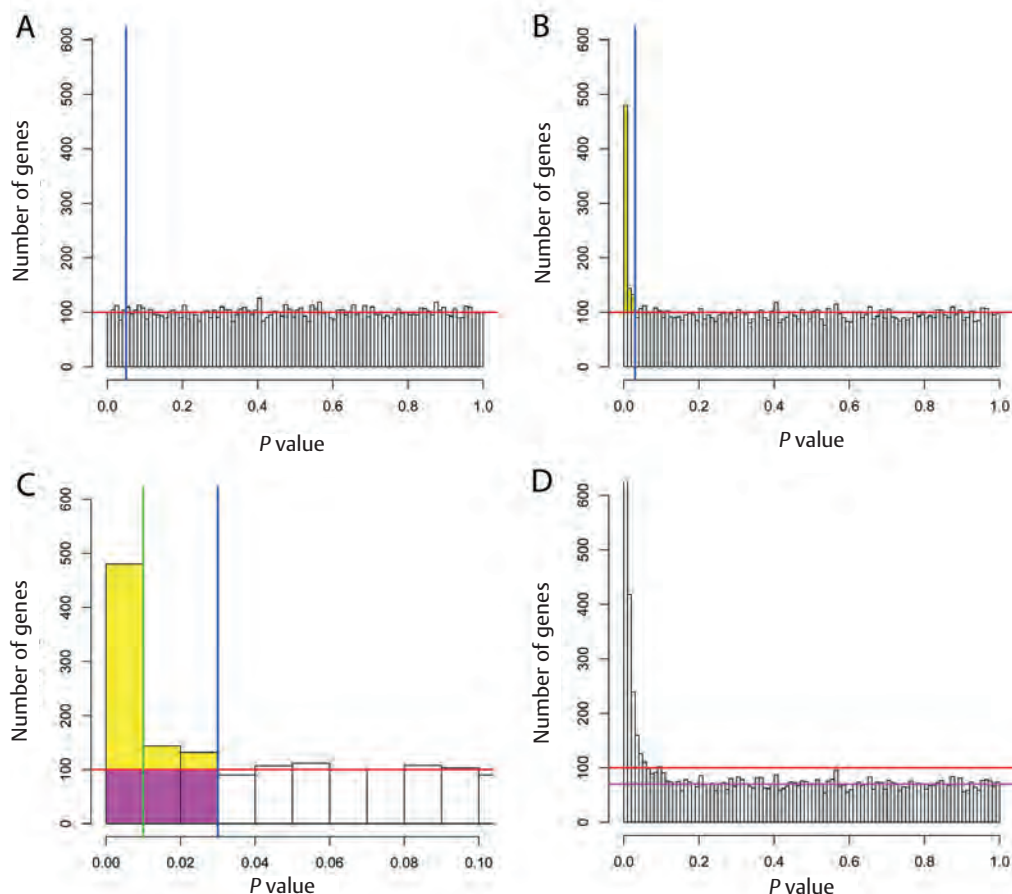
Due to the issues discussed above, multiple tests correction of the classical type are not commonly used in analysis of microarray data these days. Instead, false discovery rate (FDR) has become a standard for multiple tests correction in microarray data analysis. The idea of FDR put forward by Benjamini and Hochberg (Benjamini & Hochberg, 1995) is that it would be convenient to know what per cent of the positives discovered by

multiple significance tests are false positives:  $FDR = (\text{number of false positives})/(\text{number of all positives})$ . Let us see how this works using a simulated data set. We'll add truly differentially expressed genes to the all-null situation in Fig. 1A. In Fig. 1B, 500 null genes out of 10 000 have been replaced with 500 truly differentially expressed genes with mean differences of 2.5 and standard deviations of 1 in each tissue (genes with expression level distributions like the one in Fig. 2). We can see a substantial increase in the number of genes with  $P$  values close to zero. If we use a significance level of 0.03 (blue line), the yellow part must represent the truly differentially expressed genes, i.e. true positives. Figure 1C is a blow-up view of

part of Fig. 1B close to  $P = 0$ . The significance level of 0.03, used for arithmetic convenience in this example, selects 756 positives in this figure. The yellow part corresponds to the number of true positives (456 genes), and the magenta part corresponds to the number of false positives (300 genes). Therefore, when a significance level of 0.03 is used, the  $FDR = 300/756 = 0.40$ . Now we know that on average 40% of 756 genes are false positives (note that the number of false positives is an estimate). Similarly, if we use a significance level of 0.01 (green line in Fig. 1C), the number of true positives is 380, and the number of false positives is 100, so the  $FDR = 0.21$ . You can imagine that if our  $P$  value histogram had a

narrower interval, we could reduce the significance level further, and FDR could further decrease. In this case, 149 genes are positive at  $FDR = 0.05$ , which corresponds to a significance level of 0.000732. Then we get on average 141.5 true positives and 7.5 false positives – what a big difference from the average of 3 true positives and no false positives by the Bonferroni correction!

In addition, the FDR is more appropriate than the significance level in selecting positive genes by different criteria when we want to compare the positive gene sets. For example, we want to see the overlap between a set of genes significantly induced by drug A and a set of genes



**Figure 1.** Simulated  $P$  value distributions. A, the  $P$  value distribution of 10 000 null genes. The red line shows the estimate of the null distribution, which is a uniform distribution. Five hundred genes are estimated to be false positives at the significance level of 0.05 (blue line). B, 500 randomly selected genes from A are replaced with 500 truly differentially expressed genes whose expression level values are sampled from the distributions shown in Fig. 2. The yellow area represents the estimate of the true positives at a significance level of 0.03 (blue line). C, a blow-up image of B. The yellow and magenta areas represent the estimates of the true and false positives at a significance level of 0.03. D, 3000 randomly selected genes from A are replaced with 3000 truly differentially expressed genes whose expression level values are sampled from the distributions shown in Fig. 2. The estimate of the null distribution should be changed from the uniform distribution shown by the red line to that by the magenta line for a higher power. The null distribution estimates shown by the red and magenta lines correspond to the Benjamini–Hochberg and Storey FDR methods, respectively.

significantly induced by drug B. If the same significance level is used in selecting these two gene sets, one of them might be almost all false positives. The reliability of the overlap is consistent if both gene sets are selected using the same FDR instead of the same significance level.

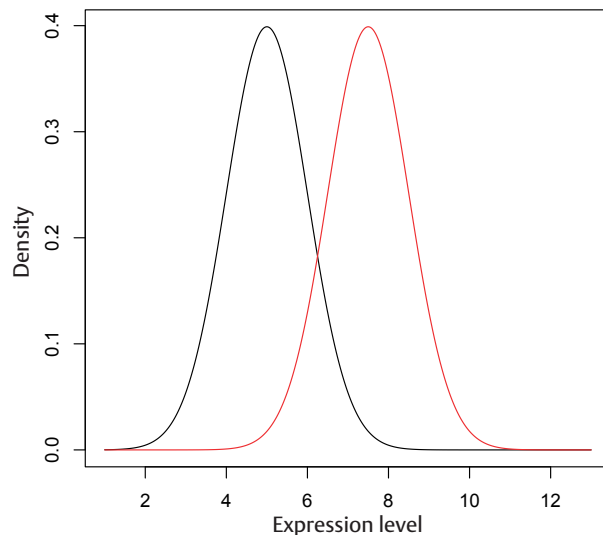
### The Storey FDR is useful when many genes are truly differentially expressed

The above FDR must be referred to as the Benjamini–Hochberg FDR since a differently defined FDR method exists. Let us consider a situation in which a relatively large number of genes are truly differentially expressed. Figure 1D shows a case in which 3000 null genes out of 10 000 were replaced with 3000 truly differentially expressed genes with expression level value distributions the same as those in Fig. 2. In this case, the red line (100 genes per interval) as an estimate of the null gene distribution appears to be an overestimate. The magenta line (70 genes per interval) is an appropriate null distribution estimate. Thus, the Storey FDR corrects the estimated null distribution of the  $P$  values when many genes are truly differentially expressed (Storey & Tibshirani, 2003). In this way, at the same FDR values, the Storey FDR corresponds to a higher significance level ( $P$  value) than the Benjamini–Hochberg FDR, hence the Storey FDR has a higher power. For example, with the  $P$  value distribution in Fig. 1D, at FDR = 0.05, 2275 positives are selected by the Benjamini–Hochberg method at the corresponding significance level of 0.0114 (2161 true positives and 114 false positives), and 2568 positives are selected by the Storey method at the corresponding significance level of 0.0185 (2440 true positives and 128 false positives).

### The $P$ value distribution for FDR correction

One big difference between FDR corrections and corrections of the old type is that FDR corrections depend on the distribution of the

**Figure 2.** The distributions of expression level values used for the simulations of the truly differentially expressed genes in Fig. 1. They have normal distributions with a standard deviation of 1, and their mean difference is 2.5.



$P$  value while corrections of the old type depend only on the number of tests. It should be emphasized that both FDR methods assume  $P$  value distributions similar to those in Fig. 1: higher closer to  $P = 0$  and flattened toward  $P = 1$ . In fact, the Storey method uses the flat part of the  $P$  value distribution to estimate the null distribution. Therefore, it is important to make sure that your data set has this kind of  $P$  value distribution before applying an FDR method. For example, when an Affymetrix GeneChip data set is preprocessed by GCRMA (Wu & Irizarry, 2004), the  $P$  value distribution tends to have a substantial peak in the middle. This is caused by the genes whose expression level values are considered to be mostly noise by the GCRMA algorithm. Therefore, such genes need to be removed before applying an FDR method.

### The $q$ value is the FDR-corrected $P$ value (sort of)

Storey also proposed the  $q$  value, which is defined for each gene as the minimum FDR that makes the gene a positive (Storey & Tibshirani, 2003). For example, a gene with  $q = 0.02$  is selected as a positive when FDR = 0.02 is used, but not when FDR = 0.019 is used. In other words, the FDR is the threshold  $q$  value: the

genes selected for FDR = 0.02 are the same as the genes with  $q \leq 0.02$ . The  $q$  value can practically (although not exactly) be considered as the FDR-corrected  $P$  value (or FDR-adjusted  $P$  value). The  $q$  value has great utility. In many cases, the information from microarray data is used to select candidate genes associated with a particular biological function, for example, genes involved in the cholesterol metabolism regulation. Candidate genes are then analysed to test for a role in the predicted function. Imagine that the throughput of our functional assay is 20 genes per month, and our project period ends in 3 months. We choose 60 genes with the smallest  $q$  values. This is no different from choosing 60 genes with the smallest  $P$  values because the conversion of the  $P$  value to the  $q$  value does not change the rank of each gene. However, with the  $q$  value, if the gene with the largest  $q$  value among those chosen has  $q = 0.017$ , we know that we expect one false positive among the 60 genes. The  $P$  value (or the  $P$  value corrected by a multiple tests correction method of the old type) will not provide such information.

### Local fdr, the ultimate multiple tests correction?

The probability that a gene with  $q = 0.02$  is a false positive if it is selected is higher than 0.02. This is



because genes with  $q < 0.02$  have lower probabilities of being false positives than this gene. Can't we estimate the probability that a particular gene is a false positive if the gene is selected? This would be the ultimate corrected  $P$  value for each gene. Such a probability is called the local  $fdr$  or gene-specific  $fdr$  (conventionally lower letters are used for the local 'fdr'). Several methods have been proposed, and they are compared in Pounds (2006). Generally, the better a local  $fdr$  method performs, the more computationally intensive it is. We are not getting into the local  $fdr$  here. However, it is likely that it will become more popular as statisticians working on microarray data recommend it. Presently, there does not seem to be agreement about

which local  $fdr$  method is the best (though see Allison *et al.* 2006).

### Using FDR methods

If R, a language and an environment for statistical computing ([www.r-project.org](http://www.r-project.org)), is used for analysis, the  $q$  values based on the Benjamini–Hochberg FDR can be calculated from a set of  $P$  values using the `p.adjust` function with an option of `method='BH'`. The  $q$  values based on the Storey FDR can be calculated using the `qvalue` function in the `qvalue` package.

### Fumiaki Katagiri

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### Undergraduates – write an article and win £500

AstraZeneca is generously supporting the career development of undergraduates studying physiology as part of their degree. From 2008 there will be two annual prizes for the best physiology-related articles written by undergraduates and published in *Physiology News*.

Undergraduate students are invited to write articles, suitable for publication in *Physiology News*, on topics which might include (but are not limited to):

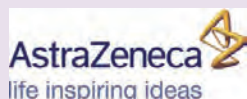
- summer/final year degree projects;
- experience of attending a workshop or conference;
- what turned you on to physiology;
- topical/current physiology-related news items;
- outreach activities (e.g. school visits, science festivals);
- research groups/activities within the department;
- review of a paper that encouraged an interest in physiology.

Articles should be submitted by **1 December 2009** and should not exceed 1000 words and can include an illustration.

Submissions should be sent to [education@physoc.org](mailto:education@physoc.org) and will be judged on appropriateness of topic and writing style by The Physiological Society's Chief Executive Officer, the Education and Membership Manager and a member of *Physiology News* Editorial Board, with agreement from AstraZeneca on the winning article.

Each prize will be £500 and a day visit to AstraZeneca's headquarters in Alderley Park, Cheshire (to include UK travel, dinner and overnight accommodation).

For full details contact Mike Collis  
([mcollis@physoc.org](mailto:mcollis@physoc.org)).



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## The Hodgkin–Huxley–Katz Prize Lecture delivered by Eric Kandel

Otto Hutter talks about their first meeting



Samyuktha Muralidharan Pillai and Eric Kandel.

To hear and meet Eric Kandel I had flown to Dublin in vain. So taking the train from Bournemouth to Waterloo and making my way past old Bloomsbury haunts to the Institute of Neurology was my second try. Over the years, from our native Vienna onwards, our paths had intersected; and in the mid-60s, when I was on the Editorial Board of *The Journal of Physiology*, we were in indirect contact. But we had never met.

I was seated early in the intimate-sized lecture hall. So I had plenty of time to contemplate the well-remembered features of Hodgkin, Huxley and Katz projected onto the wide screen. How appropriate, I thought, that Eric Kandel had been invited to give a lecture founded in honour of these famed men. For like these great knights of British physiology, Eric Kandel has applied the reductionist approach to a fundamental question; and he had learned, from their examples – as well as from Stephen Kuffler – that for every biological problem there is an organism in which it can be best studied.

While I was thus musing, Eric Kandel had started to introduce the audience to the abdominal ganglion of *Aplysia*, the preparation that had yielded to his quest into the biology of memory storage and learning at the cellular and molecular level. And soon afterwards we were presented

with an experiment of such beautiful conceptual simplicity – whatever may have been the practical difficulty – that I believe it may be regarded as the apogee of Kandelian reductionism. Having established in tissue culture that a selected synapse between a sensory and a motoneurone may be strengthened for the long-term by repeated pulses of serotonin – in substitution to the activity of a normally facilitatory interneurone – the question arose: do the structural changes so induced, which involve a chain of events leading to gene transcription and export of new proteins from the nucleus, remain confined to that synapse? To tackle this question Kandel and his colleagues grew a single sensory neurone with a branched axon that formed synapses with two motoneurons. On then applying pulses of serotonin to one set of synaptic connections, only that selected set was found to respond with growth of new synaptic terminals. Subsequent work by Kandel and his colleagues showed that an activated synapse becomes marked for the long-term by local synthesis of self replicating prion-like proteins, another surprise in a long series of astonishing discoveries.

It is not our custom to follow prize lectures with questions. When a lecture is delivered from a prepared text this can be a loss: for lecturers reveal more of themselves during questioning. This time, however, we were soon captivated by Eric Kandel's engaging personality. Belying his years, Kandel spoke scintillatingly without notes for close on an hour, at the rapid pace of a New Yorker, with shafts of humour and wit; all the while pacing the floor, turning to the audience to clarify a point, and anchored to the speakers desk only to press the button calling for the next slide. Altogether, it was an amazing feat by one soon to due celebrate as octogenarian. Of such virtuous men the psalmist says: 'They will still be fruitful in old age, vigorous and fresh they will be.' (Psalm 92). Long may these words yet apply to Eric Kandel.

**Otto Hutter**

## Otto Hutter Physiology Teaching Prize



Photo by Martin Rosenberg.

Over the past few years, The Physiological Society has taken steps to raise the profile of physiology teaching. We are now pleased to announce the launch of the Otto Hutter Physiology Teaching Prize, a vehicle for The Society to recognise an individual's contribution to teaching undergraduate physiology.

We are proud that Otto Hutter has agreed to lend his name to The Society's new prize. Otto began his career during the war as a scientific technician at the Wellcome Physiological Research Laboratories, before completing a BSc and PhD at UCL. As well as having a successful research career, Otto has helped spread physiology education to a wider world, both internationally and through teaching innovation. At Glasgow, he pioneered perhaps the first, fully integrated electrophysiological lab for junior teaching. He is also a virtuoso of small group teaching, famous for throwing the blackboard chalk as an inducement to do some of the board-work yourself!

Nominations for this prize should summarise the nominee's contribution to teaching in less than 400 words, and include details of any supporting teaching materials. Self-nominations are welcome. The recipient of the prize will receive £1000 in prize money (£500 of which should be used for teaching resources).

Nominations, or any questions regarding this scheme, should be sent to [education@physoc.org](mailto:education@physoc.org). It is now too late for the 2009 award. The winner for this year will be notified by the end of the year.

## WHO does not recommend the use of homeopathy for HIV, malaria, TB, influenza and infant diarrhoea

In the last edition of *Physiology News* (PN76, p. 35) Harriet Teare, a member of Voice of Young Science (VoYS), described how homeopaths are establishing services and clinics in Africa and claiming to treat serious diseases such as TB, HIV, malaria, infant diarrhoea and influenza. She explained how, together with their peers in Africa, VoYS had written to the World Health Organisation (WHO) calling on the body to condemn the promotion of homeopathy for treating these five serious diseases. In August they got a response from the WHO.

VoYS is a network made up of over 600 early-career researchers, set up by Sense About Science to encourage researchers to get involved in public debates about science and take responsibility for correcting scientific misinformation. The use of homeopathy to treat life-threatening diseases really concerned us; lives were at risk and we had to make a stand against it. We were disappointed to see that the WHO has no guidelines about the dangers of homeopathy with regard to serious diseases. For many people in the world, they are the only reliable source of health care information available and so they have a responsibility to issue safe guidelines about disease, based on sound evidence.

After the initial publicity of writing to the WHO, we were contacted by people from all over the world struggling with these practices and keen to hear a response from the WHO. Medics working in Africa have explained how difficult the situation is for them, with local people having little trust in Western medicine and with many people, including journalists, struggling to distinguish between real science and suspect practices.

The WHO is a large bureaucratic organisation which can be difficult to penetrate and we had to be persistent. We initially contacted the Division of AIDS, Tuberculosis and Malaria at the WHO Africa office but were redirected to several offices with no result. Determined not to give up, we

regrouped and decided it would be important to have the support of the relevant disease programme directors. Their comments would be respected as expert recommendations and advice about these diseases.

Together we contacted the Stop TB Department, the HIV/AIDS Department, the Global Malaria Programme and the Department of Child and Adolescent Health and Development outlining our concerns. The response was fantastic with some directors replying instantly. Child Health at WHO commented that *'We have found no evidence to date that homeopathy would bring any benefit to the treatment of diarrhoea in children'* and the Stop TB department claiming their treatment guidelines *'have no place for homeopathic medicines.'* All the departments responded, stressing the need for evidence-based conventional treatments. Having these comments highlights what a serious issue this. However, it required our efforts and persistence to encourage the right people in power to speak out.

We sent these comments to the WHO Director General's Office who responded, confirming that they *'clearly express the WHO's position.'* We then sent the comments to every health minister in the world, to highlight the problem and give them support to act against these practices in their countries. It will also help health care workers warn of the dangers of homeopathy and strengthen their efforts to provide evidence-based health care. Robert Hagan, a member of VoYS said, *'We need governments around the world to recognise the dangers of promoting homeopathy for life-threatening illnesses. We hope that by raising awareness of the WHO's position on homeopathy we will be supporting those people who are taking a stand against these potentially disastrous practices.'*

Our response from the WHO was one of the top five stories on BBC Online and this was followed by wide international coverage in places where we felt it really mattered including online news sites in Kenya, Ghana, Brazil, India, Argentina and Mexico. Blogs and forums were full of comments and discussions with people from all over the world debating whether this was either a bold step to improve health care or a vicious 'attack' on homeopathy.

We were surprised when a statement was added to the BBC story from the Society of Homeopaths, saying that *'There is a strong and growing evidence base for homeopathy and most notably, this also includes childhood diarrhoea.'* The studies that the Society presented in favour of homeopathy were flawed and incomplete. They were all by the same author and had not been independently replicated. They also failed to highlight another study by the same author that had a negative result. When journalists present an argument as having two sides of equal weight when in fact the evidence all falls on one side, it can be confusing and difficult to make sense of the conflicting claims. It is not always possible for the public to be able to distinguish between good and bad science and so it is exactly for these reasons that scientists need to speak out and respond to misinformation.

More importantly, if no one speaks out about these issues, people will think it is acceptable to promote untested medicines for life-threatening disease. The presence of homeopaths in Africa is undermining people's faith in conventional health care and countering the efforts of those who are trying to deliver the necessary help. These countries do not need homeopathy. They need resources like a safe water supply, vaccinations, antibiotics, trained medical staff and good health education. When homeopathy stands in place of these vital resources, lives are lost.

We have brought this serious issue into the public debate and that is a great achievement. Even as early-career scientists, we can make an impact and raise awareness of these issues. You can get large authorities to speak out; it just requires patience and persistence. As Raymond Tallis said, *'It illustrates the importance of young scientists, torchbearers for a better future, taking a stand and speaking out.'*

The more members we have in our network the bigger an impact we can make on these projects. If you want to join the network, or to find out more about VoYS, the workshops we hold and the publications we've produced please visit [www.senseaboutscience.org](http://www.senseaboutscience.org) or contact Julia at [wilson@senseaboutscience.org](mailto:wilson@senseaboutscience.org)

**Julia Wilson**  
Sense About Science



## Charles Darwin and The Physiological Society

The year 2009 marks the bicentenary of the birth of Charles Darwin (12 February 1809–19 April 1882), as well as the 150th anniversary of the publication of his most celebrated work, *On The Origin of Species*, which went on sale to booksellers on 22 November 1859. Given the central position of evolution and natural selection in our understanding of biology, Darwin has a strong claim to be the greatest of all biologists. Both *Science* and *Nature* published a range of features celebrating the anniversary of his birth early this year, as did most newspapers.

Much of the above will be known to many, or even all, readers. Some will also know that Darwin was a friend of the founders of The Physiological Society, and was elected as one of the first two Honorary Members of The Society at The Society's third ever, and first formal (with a rule book) meeting. But Darwin's connections with The Society, and its early Members, also encompassed many detailed scientific exchanges. Following his early voyages, Darwin spent most of his later career in his home at Down House in Kent, maintaining a voluminous scientific correspondence and many scientific collaborations. The Darwin correspondence project [1] tells us:

"Darwin exchanged letters with around 2000 individuals over his lifetime...He rarely attended meetings of scientific societies, typically spent only two weeks a year in London, and only occasionally received fellow scientists into his home. And yet he was arguably one of the best informed scientists of the day..."

Darwin's long-term correspondents included John Burdon Sanderson, Professor of Physiology at UCL and latterly in Oxford, with whom Darwin discussed electrical signals in plants. Michael Foster, the founder of the Cambridge Physiological Laboratory, discussed curare with Darwin. A younger physiologist who corresponded with and visited Darwin frequently was George Romanes (1848–1894), who studied the locomotory system (muscles and their control) of *Medusae* (jellyfish).

Darwin's interactions with Sanderson, Romanes, Foster and others amongst the founding Members of The Physiological Society, are well described in a fascinating 1970 article by RD French, "*Darwin and the physiologists, or the medusa and modern cardiology*".



Romanes' work on jellyfish had a particularly clear evolutionary underpinning, as the analogies of the jellyfish "muscular bell" with rhythmic muscular systems in higher animals were clear. French explores the influence of Romanes' ideas upon the theories of cardiac conduction and rhythmicity then being developed by WH Gaskell and others. Darwinian influence is clear in the opening words of Gaskell's celebrated August 1883 paper, written little more than a year after Darwin's death:

"The views held by physiologists upon many points connected with the innervation of the heart have been too exclusively based upon observations upon a single type of heart, viz. that of the frog. It is therefore very advisable wherever possible to control these experiments by a corresponding elaborate series of observations upon the hearts of a large number of other animal types, and in this way to trace the evolution of function in the same way as the morphologist tracks that of structure."

Perhaps Darwin's greatest gift to physiologists was his unequivocal support for animal experiments as a way of making advances in physiology and medicine. The founding of The Physiological Society was a direct result of the late Victorian vivisection controversy, and the 1875 Royal Commission on vivisection. Those unaware of this history can find a summary of it on The Physiological Society website under "About: History". The Commission's report became the basis for the Cruelty to Animals Act of 1876, which established the system of licences for experiments on living animals. Darwin gave evidence in person to the Royal Commission, stating his belief in the need for animal work:

"I am fully convinced that physiology can progress only by the aid of experiments on living animals. I cannot think of any one step which has been made in physiology without that aid. No doubt many surmises with regard to the circulation of the blood could be formed from the position of the valves in the

veins, and so forth, but certainty such as is required for the progress of any science can be arrived at in the case of physiology only by means of experiments on living animals."

Darwin went on to clarify that he was referring to experiments in which animals were properly anaesthetised, and to express his surprise at objections to such procedures:

"It is absolutely unintelligible to me on what ground the objection [to these experiments] is made in this country."

The physiologists were very appreciative of Darwin's support. The first informal meeting to discuss the founding of The Physiological Society, which took place at Burdon Sanderson's London home on the 31 March, 1876, was attended both by Darwin's most prominent scientific disciple, Thomas Huxley, and also by Darwin's third son Francis Darwin (1848–1925), then 28 years old. Francis Darwin, who assisted his father in much of his research and ultimately became a distinguished botanist and FRS, had been working for his MD thesis in one of the London physiological laboratories. The meeting reconvened a few weeks later on 26 April, with Huxley chairing, to ratify a rule book, including the rule that:

"Men of distinction in Science who have contributed to the advancement of Physiology are eligible for election as Honorary Members."

The third preliminary meeting, held at Romanes' house, identified those "who shall be invited to become Members and attend the next meeting of The Society." This group included both Thomas Huxley and Francis Darwin. The meeting also resolved to elect Charles Darwin as one of the first two Honorary Members (the other was William Sharpey).

Darwin wrote to Romanes on 29 May: "I was very much gratified by the wholly unexpected honour of being elected one of the Honorary Members [of The Society]. This mark of sympathy has pleased me to a very high degree".

Darwin remained unswerving in his support for animal experimentation until the end of his life. A celebrated letter he published in *The Times* in 1881, runs:

"I know that physiology cannot possibly progress except by means of experiments on living animals, and I feel the deepest conviction that he who retards the progress of physiology commits a crime against mankind."

This letter can be read at the *Times* online archive [2], along with accompanying material and a commentary by former Physiological Society President and ex-Head of the MRC Colin Blakemore.

Darwin's death in 1882 was a cause of great sorrow among the scientific men of the day, including at The Physiological Society. Sharpey-Schafer in his history of The Physiological Society records the feeling of the Members present at the following meeting:

**"With respect to [Charles Darwin's death] the draft of a resolution occurs in the Minute Book, written in pencil and nearly illegible, which probably expresses an attempt then and there to voice the feelings of The Society... The draft reads as follows: 'The effect produced in the scientific world by the death of Charles Darwin is so universal and profound that any formal motion in reference to it by this little Society would appear to be superfluous, if not impertinent.'"**

The same meeting in 1882 elected several new Honorary Members including, perhaps a little symbolically, Thomas Huxley. Huxley and Francis Darwin attended several Society Meetings, and physiology in the late 19th and early 20th century was also indebted to Darwin's fifth son Horace (1851–1928), founder and long-time director of the Cambridge Scientific Instrument Company. Sharpey-Schafer's history makes clear that the approbation and involvement of men of the standing of Charles Darwin and of Thomas Huxley was of the greatest importance to the fledgling Society.

Perhaps an appropriate place to close this brief summary of Darwin's ties to The Society is an editorial in *Science* earlier this year by past President of the Royal Society Robert (Baron) May and Paul Harvey, who drew attention to:

**"...Dobzhansky's memorable injunction that nothing in biology makes sense except in the light of evolution."**

This insight can be seen running through papers in The Physiological Society's journals from the 1870s to the present day. It will doubtless continue to do so long into the future.

French RD (1970). *J Hist Biol* 3, 253–274.  
Gaskell WH (1883). *J Physiol* 4, 43–230  
May RM & Harvey PH (2009). *Science* 323, 687.  
Sharpey-Schafer E (1927). *J Physiol* 64 (Suppl), 1–76.

[1] [www.darwinproject.ac.uk/content/section/17/112](http://www.darwinproject.ac.uk/content/section/17/112)

[2] <http://timesonline.typepad.com/timesarchive/2009/02/video-ben-macin.html>



## Biosciences community unites to launch Society of Biology

The two leading UK biology organisations – the Institute of Biology (IoB) and the Biosciences Federation (BSF) – have united to form the Society of Biology.

An Interim Council has been operating for almost a year to develop the structure and objectives of the Society, and the Council of the Society of Biology met for the first time on the 7th October. Dame Nancy Rothwell is the first President, William Marshall, the Honorary Treasurer, and David Coates, the Honorary Secretary.

The creation of a single organisation to represent the biological sciences has been fully supported by members of both the IoB and BSF, who voted overwhelmingly in favour of the move at Annual General Meetings held in early 2009. The Society's diverse membership includes students, practising scientists and interested non-professionals – as individuals, or through learned societies and other organisations.

Commenting on the launch of the Society, Nancy Rothwell said, 'It is wonderful that the Society of Biology has been established in the year that we are celebrating Charles Darwin and all that he achieved and changed. The Society will be fully inclusive and aims to engage with all, including the most prestigious academics, school teachers, policy makers, funders and the committed (and often expert) non-professional biologists.'

The Society's first Chief Executive, Mark Downs, has been in post since the 1st November. Dr Downs was previously the Director of Science and Enterprise at RNID, and has significant experience in science policy in the government, private and academic sectors.

The Society's mission is to create a single unified voice for UK Biology that will build on and develop the strengths of the IoB and BSF. The aim is for the Society to be fully inclusive in



Mark Downs.

welcoming non-professional as well as professional biologists of all ages and backgrounds. All current members of the IoB and BSF will automatically be transferred to the Society and individuals will retain their postnominals, updated to reflect Society of Biology membership. The interests of members will be represented by two Colleges: the College of Individual Members and the College of Organisational Members. Each College will elect a Chair who will serve on the Society's Council.

During the first year, the Society of Biology will pay particular attention to consulting with its members and partner organisations about their expectations for the Society, and will identify how it can deliver further services for members. It will develop regional bases across England, Wales, Scotland and Northern Ireland and seek new partnerships in the UK and overseas. The Society will further develop its role as a key advisor to government, funders and policy makers on all relevant activities – a role previously held by the integrating organisations. An area of focus will be education at all levels, lifelong learning, continuing professional development and chartered status.

Sir Paul Nurse, Nobel laureate and President of the Rockefeller University, said: 'The establishment of the Society of Biology is a significant event for UK biosciences. The field of biology encompasses a wide diversity of disciplines. The creation of a single organisation will enable stronger, more effective representation, and will serve all with an interest in the future of the biosciences.'

We welcome suggestions for the Society of Biology. For more information see the website: [www.societyofbiology.org](http://www.societyofbiology.org)

**Emma Southern**





## Musings from the Chief Executive's desk

It's been a busy few months since our Main Meeting in July. Looking back at Dublin, I was really impressed by the quality of the science presented and by the number of top-flight international speakers who participated. I think that money spent on bringing the best speakers to our meeting is money well spent and that we should do more of it. It was also good to see a number of Members of the Editorial Boards of both our journals at the meeting. Their active support and involvement in Society meetings is always very welcome. The only downside I remember was the expense of being in Dublin, exacerbated by a poor exchange rate. Paying over £5 for a pint of Guinness is hard to swallow (sorry!).

Early September saw the joint meeting with the BPS on "Integrative Pharmacology and Physiology – translating 'omics' into functional and clinical applications" held at King's College London (see a report on the meeting on p. 9). This was the first time I have organised a meeting from 'soup to nuts', as the expression goes, and I found it an exhausting but very satisfying experience. Much of the penultimate work on the meeting had to be done remotely, as I was away on my summer holidays during August. The world-wide availability of electronic communications is perhaps a mixed blessing when one is on holiday, but I was very happy with the result. Over 180 physiologists and pharmacologists attended the meeting and 83 abstracts were presented for poster or oral communication. The meeting certainly demonstrated that *in vivo* physiology and pharmacology is alive and well in the UK. The standard of the talks presented was high and I was able to use my role as 'holder of the roving microphone' to sneak in my own questions to nearly all the speakers. The disruption to

my holiday and my family's cries of "Michael, you are not supposed to be working" were worth it after all.

The joint meeting with the BPS was also my first experience of participating in a podcast. I am usually the last person to adopt new technology and am perversely proud not to own a 'pod'. I come from a generation where you listen to music on speakers where size really does matter. I tend to think that people who walk or cycle around listening to minute headphones are significantly more likely to be involved in accidents and therefore give them a wide berth. However, I have to report that making a podcast was remarkably painless and I felt quite proud of the result – although I still don't plan to buy an iPod!

Continuing on the topic of new technologies and reformed luddites, I am also very impressed with the number of Members who are now fans of The Society on Facebook. Having avoided social networking sites myself for some years (I only joined Facebook this year to sneak a look at my children's photos) I have to say that The Society page is excellent. It looks like a great way for Members to comment on what The Society is doing and to make suggestions on what else it could do to support them. We don't get enough feedback from our Members and I encourage you to sign up and use this site to tell us what is on your mind.

Another activity that has been occupying me recently has been The Society's long-term business plan (see *Physiology News* 75). Following the discussions at Council, a number of proposals for how The Society could develop over the next 5 years have been prepared and have now been discussed and reviewed with Society staff, to get their views and input.

The plan that is developing contains a large number of interesting and novel proposals. The Society is already successful and influential

and the long-term strategy is to build on existing success rather than to re-invent the wheel. No single area of The Society's activities is seen as having the greatest future priority as they are all important, and all have the potential to grow, but there is an overall goal developing to increase our activity in clinical and translational science. One way to encourage this development is by increased interactions with organisations such as the Academy of Medical Sciences and by encouraging clinically qualified/aligned scientists to join The Society and to put themselves forward for membership of Council. Another important goal is to increase our media presence to clearly demonstrate the importance of physiology to the public and to key decision makers in government and educational establishments. Consequently we plan to take steps to increase the media coverage The Society gets for papers in its two journals and for all of its other activities.

An important organisational objective that has received significant support in these long-term planning discussions is to purchase or rent office accommodation in London that can house all Society staff, combining our London and Cambridge offices. Establishing a 'home' for The Society could have the added benefits of providing a meeting room large enough for Council meetings, small scientific meetings and workshops with additional facilities for Members, such as hot-desks with computers. Would you like to see The Society housed in a single building with a range of facilities available for our Members, and what would these facilities be? The timescale for this move is likely to be 3–4 years and we will be surveying Members' views on this in the future. However, your input is always welcome so please do email me about this proposal at any time.

**Mike Collis**

# The Journal of Physiology

## New Editors

### Nisha Charkoudian



The focus of Dr Charkoudian's research is on sympathetic neural control of the circulation in humans, as related to the regulation of blood pressure and body temperature in healthy humans as well as in obesity, hypertension and type 2 diabetes. She is interested in interactions between humoral control of blood volume (e.g. angiotensin II) and sympathetic neural control of arterial pressure, as evaluated using direct microneurographic measurements of sympathetic neural activity. Another focus of the laboratory is the evaluation of mechanisms of thermoregulatory control of the skin circulation in type 2 diabetes mellitus. Ongoing studies include evaluations of the role of endogenous angiotensin in altering sympathetic nerve activity, the roles of systemic inflammation in altering control of sympathetic nerve activity and blood pressure, and the importance of inter-individual variability in sympathetic neural and haemodynamic variables in the control of blood pressure in humans. Dr Charkoudian is Associate Professor of Physiology in the Department of Physiology & Biomedical Engineering, Mayo Clinic College of Medicine. She also has a joint academic appointment in the Department of Anesthesiology, and her research involves collaborations with investigators in the Departments of Anesthesiology, Neurology and Medicine (Division of Endocrinology).

### Paul R Martin



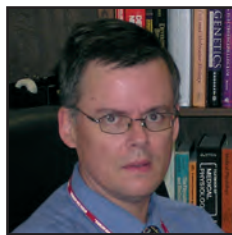
Paul Martin is Director of Research at the National Vision Research Institute

of Australia and Professorial Research Fellow at the University of Melbourne. He read Physiology and Psychology at the University of Sydney and received his PhD in Physiology at Sydney in 1986. Following postdoctoral work in Germany, in 1992 he joined Faculty at the University of Sydney. He took up his current appointment in Melbourne in 2002.

His abiding research interest is signal processing in nervous systems, with experimental expertise in function and connectivity of afferent visual pathways. His research programs have addressed how signals from receptors in the eye are fed into separate brain pathways which underlie the red-green and blue-yellow axes of colour vision. Because defects in colour vision are an early sign of blinding diseases such as glaucoma, basic experiments such as these can improve our understanding of visual dysfunction, as well as revealing the basis of the colour sensations which so enrich our perception of the world.

Results of these scientific experiments have been published in over 60 papers in scientific journals and several textbook chapters. More information can be found at the National Vision Research Institute ([www.vco.org.au/nvri](http://www.vco.org.au/nvri)).

### Mark Nijland



I was born in Manzini, Swaziland and grew up in Swaziland and South Africa. I am married with two children (son 12, daughter 17). I obtained a BSc in Zoology and Physiology at the University of the Witwatersrand in Johannesburg. I continued at Wits School of Medicine where I obtained a BSc Hons in Animal Physiology and PhD (1988) in Physiology entitled 'The Mechanism and Function of Selective Brain Cooling in sheep (*Ovis aries*)', supervised by Drs Duncan and Graham Mitchell. After a brief time away from science working in the computing industry, I undertook

postdoctoral training in exercise and thermoregulation with Dr Mary Ann Baker at the University of California Riverside. I then moved to the Department of Obstetrics and Gynecology, UCLA (1992) and began my career in fetal physiology. There I developed my interests in cardio-renal development and the development of dipsogenesis thirst. I joined Dr Peter Nathanielsz at Cornell University in 1996, where the impact of antenatal steroid therapy on the developing cardiovascular system became an additional focus. Today I study the contribution of maternal nutrition, both in excess and insufficiency, on fetal brain and cardio-renal development and their contribution to cardiovascular and renal disease susceptibility in later life. I am currently an Associate Professor and the Scientific Director of the Center for Pregnancy and Newborn Research, affiliated with the Division of Maternal Fetal Medicine in the Department of Obstetrics and Gynecology, University of Texas Health Science Center at San Antonio. I am an author of 80 journal articles, 120 conference abstracts and 4 book chapters.

### Harunori Ohmori



Professor and a chairman of the Department of Physiology and Neurobiology, Faculty of Medicine, Kyoto University.

Our laboratory activities are focused on the understanding of mechanisms of hearing on the basis of synapse and neuronal activities. Our first work on hearing was made on isolated hair cells, focusing on membrane excitability, the mechano-electrical transduction, and the release of neurotransmitters. After a series of works on hair cells, our interests moved to neural circuits, particularly of the auditory system, in order to understand how sound information is processed in the brainstem auditory nuclei; a mechanism of sound source localization in whole animals, and the cellular mechanisms using brainstem slice preparations on how the precise coincidence detection is achieved in auditory nuclei.

From the laboratory, we have a cat at home, which came to our place, along with other cats, after the big earthquake in Kobe 1995; he is now a big cat and alone, but disciplines us in the house and urges us to wake up in the morning and go to bed at night. My wife and I like bicycling around the city and enjoy photography, especially of the cherry blossom in spring and the coloured leaves in autumn in scenes with old temples and shrines.

### Bente Klarlund Pedersen



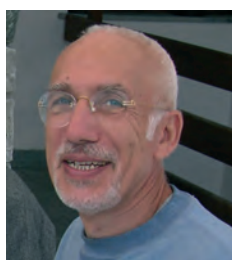
Bente Pedersen is Professor of Integrative Medicine and a specialist in infectious diseases and internal medicine. She is the Director of the Danish National Research Foundation's Centre of Inflammation and Metabolism (CIM): 6 senior researchers, 9 postdocs, 15 PhD students, a technical staff of 8 persons and 12 pre-graduate students or research assistants.

BKP has identified skeletal muscle as an endocrine organ that produces and releases signal peptides, which are named 'myokines'. Given that skeletal muscle is the largest organ in the human body, the discovery of contracting muscle as a cytokine-producing organ opens up a whole new paradigm: Skeletal muscle is an endocrine organ, which, by contraction, stimulates the production and release of cytokines, which can influence metabolism and modify cytokine production in tissues and organs.

BKP has had many positions of trust. She has served as President for the International Society of Exercise and Immunology, President for the Danish Society of Infectious Medicine, Chairman for the research council at Rigshospitalet, coordinator of the Muscle Research Cluster at the Faculty of Health Sciences, University of Copenhagen and as President for the National Council for Public Health in Denmark.

### Carlo Reggiani

Carlo Reggiani is Professor of Physiology at the University of Padova,



Italy, teaching medical students and those on exercise and sports sciences courses. He is also Director of the Sport Medicine School at Padova.

Carlo studied medicine at the University of Pavia, graduating in 1972. After a few years at the University of Lund in Sweden, working in the laboratory of Professor P Edman, he was appointed Associate Professor of Physiology back at Pavia in 1983.

His main physiological interest is the biophysics and physiology of skeletal and cardiac muscle, in particular the relationship between myofibrillar proteins, and their isoforms, and contractile performance, and the regulation of myofibrillar protein expression under certain functional conditions. He is funded by European Union grants, Telethon (an Italian charity supporting research in muscle pathophysiology) and the Italian Space Agency (ASI).

### Matthew Watt



Matthew Watt completed postdoctoral work at the University of Guelph and McMaster University, Canada. His work during this time focussed on the factors that break down fat in muscle, particularly during exercise. Upon returning to Australia, Dr Watt worked at RMIT University and in the Protein Chemistry and Metabolism laboratory at St Vincent's Institute. He worked extensively on identifying how defective fatty acid metabolism interacts with inflammatory processes and deciphering ways to circumvent these inter-related health issues. Dr Watt currently heads the Biology of Lipid Metabolism group at Monash University, Victoria, Australia. He has published 72 papers/review articles

and is currently funded by the National Health and Medical Research Council of Australia, the Australian Research Council and the Diabetes Australia Research Trust. The general aim of Dr Watt's research is to study how fats are broken down in muscle, liver and adipose tissue and how these processes can be made more efficient. He also studies how defects in fatty acid metabolism contribute to the development of insulin resistance. This research has direct implications for people with obesity and type 2 diabetes, who store more fat and are less able to burn fat. Dr Watt's other job is listed as a 'sports tragic', where he donates an enormous amount of time dragging his children to Australian Rules football matches.

### Ulf Ziemann



*Current position:* Associate Professor of Neurology and vice-director of the Department of Neurology, and Head of the Motor Cortex Research Group, Goethe-University of Frankfurt, Germany. *Special clinical interests:* multiple sclerosis, motoneuron diseases, clinical neurophysiology. *Special research expertise:* Systems physiology of human motor cortex. Excitability, connectivity, plasticity and learning processes in human motor cortex. Pharmacological modulation of motor cortex excitability and plasticity. *Methodological expertise:* Transcranial magnetic and electrical stimulation, EEG, MEG, MRI, fMRI, diffusion tensor imaging, EMG, neuropharmacology. *Prizes:* Fellow of the German National Academic Foundation, NIH Fellowship Award for Research Excellence, NIH Merit Award, Richard-Jung-Prize 2006 of the German Society of Clinical Neurophysiology and Functional Neuroimaging. *Editorships:* Associate Editor of Clinical Neurophysiology, Deputy Editor of *Brain Stimulation*. *Memberships:* The Physiological Society, Society for Neuroscience, Movement Disorder Society, German Society of Clinical Neurophysiology and Functional Neuroimaging, German Society of Neurology.



## Snakes and ladders

As someone who frequently uses the 'ping' of a new email to distract me from paper writing, I saw that I had received one from The Physiological Society's Human Physiology Special Interest group. Immediately, I opened it, anticipating an interesting but transient diversion. However, on this occasion I saw that the beloved beeb (BBC) were on the lookout for someone to help with a programme investigating the autonomic responses one associates with fear. As the paper I was happy to be distracted from was the final draft (hopefully) of an investigation of the relationship between autonomic responses, the fear of falling and locomotor behaviour, I was a little taken aback.

Upon further reading and the realisation that perhaps I should step up to the plate and offer my assistance I had a fearful experience of my own. After all, I had the kit (with a little help from my friends), the flexitime (the term had ended) and the knowledge (well hypothetically at least). So after a bit of soul searching and discussion with colleagues, all of whom said it would be great for the career and with a little trepidation I offered my 'services', although I felt sure that the beeb would surely choose not to use them.

Strangely, they said 'thanks very much'. Following an email exchange, finally a few sketchy details emerged: they wanted to measure autonomic parameters *aka* the typical flight-or-flight responses from a presenter getting up close and personal with a snake in a cave – at which point I too started to experience significant fear responses. However, it was too late now to back out. After much to-ing and fro-ing, the location was set as a cave in Painshill Park, Surrey – they were going for the Indiana Jones snake pit look, ummmm....

So having checked and then double-checked the equipment, bright and early I drove off in the uni van (an Aussie ute without apparent gear box or brakes) to be met on location



by a fellow Physoc Member, James 'Jim' Clark, whose assistance on the day was absolutely invaluable. Upon our arrival 'on set' an extremely warm welcome was received, mainly due to relief in the fact that we had actually found the place. Then following protracted reciprocal wonderment of each others' equipment and the rather strange but beautiful grotto (think half cave, half man-made gothic cathedral, not a large man in red suit and white beard) was complete – scientists and crew got to work.

Having overcome light, water, power, camera, angry non-informed tour guide, presenter and snake issues, filming began. Now call me naive but I was expecting a filming process where instructions would be barked, clapper boards would be, well clapped, and we did our science bit in between. In reality everything was a little freestyle, with the distinction between Jim, and the actual director, who disappointingly came without a cravat or foldable chair, becoming increasingly blurred. Attempts at scientific rigour and any real explanation took a back seat, although we did get the job done and some representative responses were acquired – an extremely large snake around your neck is quite a potent physiological stimulus!

I took my turn in front of the camera – although in a purely non-speaking role and well away from the beautiful yellow Burmese python called Rah, yes really, provided by the lovely

Snakey Sue (available for children's parties). Upon packing up we were informed that the programme was intended to be the replacement for *Tomorrows World*, but some highly paid media types had decided to update the name to '*Bang goes the Theory*'. To our relief the title is misleading in that its premise is not to disprove conventional scientific thought – a generally healthy attitude, but not when it is me on the TV!

I guess the fact I was referred to as Dr Dave on camera is symbolic of the 'level' it is pitched at – horizon it isn't. Further filming at the UCL Institute of Cognitive Neuroscience was to follow so perhaps the hard science shall come from there. Anyway, I'm sure my friends, colleagues and family will all find it hilarious. Let's just see if the old adage – any publicity is good publicity – holds true. As for a career in the media – let's just say my agent (Physoc) is still waiting by the phone, so I am sure Lord Winston can sleep soundly in his bed. Apparently, I have a face for radio.

The experience was great fun, although scientifically a little frustrating. As to whether for my real career it is a snake or a ladder, only time will tell.

### Dr Dave

Dr Dave and the snake story was broadcast on BBC 1 on Monday 24th August 2009 as part of the *Bang goes the Theory* series. ([www.bbc.co.uk/bang](http://www.bbc.co.uk/bang))

**David Andrew Green**  
King's College London

## Physiology News

If you have enjoyed this issue of *Physiology News* please don't throw it away. Put it in your coffee room so that others may see it too.

We are always looking for interesting features, meeting reports, news items and photographs. Contact The Physiological Society Publications Office ([magazine@physoc.org](mailto:magazine@physoc.org)) with your suggestions.

## XIth Little Brain Big Brain Meeting



View of Kenosha port from the conference hotel.

The city of Kenosha, situated on the shores of Lake Michigan, was the setting for the XIth Little Brain Big Brain (LBBB) meeting, held on the 24–26th August 2009. This bi-annual event exists as a forum for early-stage researchers working in neurogastroenterology to come together with their peers and discuss their work. Now in its 20th year, the LBBB is a prestigious meeting and competition for places via juried applications was fierce. This is no surprise when you consider that the alumni of previous LBBBs include many of our current senior researchers, and from whose labs many of this year's attendees were chosen.

However, the meeting itself was held in a relaxed and convivial atmosphere, with ample opportunity for exchanging ideas and germinating collaborative links. Participants were limited to 38 delegates, ensuring that each person could present their work and receive maximum feedback through protracted post-presentation discussions. The emphasis placed on these discussions is the hallmark of the LBBB and differentiates it from other scientific meetings. Each 15 min presentation is allocated an equivalent discussion period, but this was frequently exceeded, with

some debates lasting 40–45 min. Consequently, the meeting schedule was designed to cope with this need for flexibility. Furthermore, LBBB presenters are encouraged to discuss work in progress or research that they wish to develop into independent projects. It is this combination of debate and of sharing new data that makes the LBBB an innovative forum in which to shape future research ideas and goals.

This year's organisers, David Linden, Simon Gibbons and G. Richard Locke (Mayo Clinic, USA), did a tremendous job in managing this event and ensuring that it adhered to the traditions of previous meetings. Simon Brookes (Adelaide, Australia) and Helen Raybould (UC Davis, USA) moderated the sessions brilliantly, allowing all the participants generous time to air their views.

Sponsorship for these events is essential to ensure their survival and this meeting received superb funding. The Physiological Society provided sponsorship directly to the meeting and also provided a generous travel grant for myself. In addition, the European Society of Neurogastroenterology and Motility, the German Society of Neurogastroenterology and Motility and the American Neurogastroenterology and Motility Society, as well as the American National Institutes of Health were also pivotal in supporting this meeting. The next LBBB is already being planned for Australia in 2011, where the next set of early-stage researchers will have their chance to benefit from attending this excellent event.

**Christopher Keating**  
University of Sheffield, UK



Conference delegates.

## Society Noticeboard

### Scientific Meetings 2009

For a comprehensive overview visit the website

#### An introductory workshop on human and clinical physiological techniques

King's College London and Imperial College London (10–11 Dec)

#### Cellular & Integrative Neuroscience Themed Meeting

Cardiff University, UK (14–16 Dec)

### The Journal of Physiology Symposia 2010

#### Regulation of neuronal cell volume: from activation to inhibition to degeneration

26 April, Experimental Biology 2010, Anaheim, CA, USA

#### Neural processes of orientation and navigation

2 July at Physiology 2010, Manchester, UK.

For full details of this and other Symposia visit <http://jp.physoc.org>

## 2010

#### Metabolism & Endocrinology Themed Meeting

Astrazeneca, Macclesfield, UK, 24–26 March

#### Physiology 2010 – University of Manchester (30 June to 2 July)

Abstract submission and registration opens on 1 March 2010

#### Cardiac & Respiratory Physiology Themed Meeting

University of Birmingham, 1–3 September

## Non-Society meetings

#### Life Science Careers Conference 2009

25 November, King's College London

#### BPS Winter Meeting 2009

Hilton Metropole, Brighton, UK, 15–17 December

#### Joint Annual Meeting of the Scandinavian and German Physiological Societies

27 March to 30 March 2010

#### Travel Grants

[www.physoc.org/grants](http://www.physoc.org/grants)

## Coming in from the cold: physiology at the Cheltenham Festival

When TV presenter Ben Fogle and Olympic Champion James Cracknell rowed across the Atlantic in 2005, the pair had little time to prepare for the physical and mental challenges of the race; as a result they had to overcome dehydration, sleep deprivation and a lack of appropriate clothing to complete the journey in just over 49 days. When they decided to team up again to race to the South Pole earlier this year, they had learned the importance of understanding how the body responds to extreme exercise in a hostile environment and were determined to prepare as fully as possible, with the help of clinicians, survival experts and physiologists.

The two spoke about their preparations for the Race to the Pole and their experiences in Antarctica at this year's Cheltenham Science Festival. They were joined at the festival by Dan Martin, an expert in altitude medicine from UCL, and the session was chaired by Bristol University academic and TV presenter Alice Roberts. The Physiological Society was one of the main sponsors for the event, which drew a capacity crowd on a cool and rainy Sunday evening last June.

Both Ben and James spoke very informally and openly about their adventures. Their conversation was illustrated one minute with breathtaking photographs of spectacular Antarctic snowscapes and the next with close-up shots of frozen eyelashes or gruesome blisters. They described their first exposure to Antarctic weather conditions thousands of miles from the South Pole in a cold chamber in Wiltshire, their novice experiences of cross-country skiing and their training sessions pulling tyres along the beach to simulate the weight of the pulks, or sleds, they would pull across the snow. They also discussed their search for a third team member to join them in the Race to the Pole. Originally, the actor Jonny Lee Miller was due to complete the team, but

when he had to pull out because of work commitments, Ben and James opened the place on their team to general competition and eventually chose Ed Coats, a clinician from Bristol, to join the expedition. Although lacking the Hollywood credentials, Ed had valuable medical expertise which ultimately proved more useful during their month-long trek across the snow and ice.



Ben Fogle and James Cracknell. Photo by Alexis Girardet.

In the run-up to the race itself, physiologists measured an array of cardiovascular and respiratory variables in each of the team members as they walked on treadmills in the cold lab or submerged themselves in icy water; core temperatures were also monitored, as well as peripheral temperatures on vulnerable areas like the feet and fingers. Ben Fogle admitted that one of his greatest fears during the race had been getting frostbite on his nose! The extreme cold in Antarctica was one of the main challenges of the 495 mile trek. The South Pole is a high windswept plateau at an altitude of ~2900 meters, so the team also had to cope with the potential effects of hypoxia and, as the sun never set during the period of the race, the dangers of sunburn and dehydration. Dan Martin spoke of his own experiences on Everest, and explained the unique challenges of exercising in such an inhospitable environment. He also emphasised that the success or failure of an expedition can rest on such basic essentials as a pair of dry socks! The energy demands of routinely skiing for up to 16 hours of every day was also a challenge. Ben, James and Ed followed the advice of Scandinavian survival experts and kept their energy levels up by eating bite-sized chunks of salami, chocolate, cheese and jelly babies

as they skied – these were usually eaten in the same mouthful though, as the pieces had been warmed up in transit, then fused together in the freezing temperatures. Despite these high-energy snacks and the hot meal they ate at the end of each day, the three-man team lost a total of 7½ stone in weight during the 25 days of the race. This is not surprising when you consider that

Mike Stroud, a clinician with an interest in physiology, calculated that he had used over 11 500 calories on one single day when he trekked across Antarctica with Ranulph Fiennes in 1991.

The talk was a springboard for a broad-ranging discussion of 'extreme physiology'. The general audience raised interesting questions on the difference between frostbite and frostnip, the problems of remaining hydrated when all available water is frozen, and the psychological challenges of maintaining motivation when even your iPod has given up. The energetic discussions arising from these questions illustrated clearly how an understanding of physiology is integral to the science of survival.

Compared to Scott and Amundsen almost a century ago, Fogle, Cracknell and Coats had all the benefits of modern science and technology to support them in their endeavour. The other five teams also made use of the same scientific and technological advances though, and in an echo of that epic race to the South Pole in 1911, the British team had to take second place to their Norwegian opponents. Science may march on, but sometimes history repeats itself anyway!

**Sarah Hall**



## Young Physiologists' Symposium, Dublin

On July 7th 2009, a group of early-career scientists from University College Dublin hosted a Young Physiologists' Symposium (YPS) in the new School of Medicine and Medical Science.

The symposium, entitled 'Muscle physiology: function and dysfunction', drew delegates from all over the world and provided a good start to Physiology 2009, The Society's Main Meeting.

The day started with an opening note from Paul McLoughlin, Head of Physiology at UCD, and was followed by six oral presentations on the theme of 'skeletal muscle in health and disease'. Following a short break, the theme of skeletal muscle continued, mostly focusing on human physiology. The afternoon session began with four oral presentations from young, energetic smooth muscle researchers. Each of the oral sessions prompted a lot of questions and discussions amongst the audience.

The morning and afternoon themes were neatly divided by lunch and a poster session, at which 30 scientists presented their work on skeletal and smooth muscle physiology.

The day was brought to a conclusion by Noel McHale, from the Smooth Muscle Research Centre, Dundalk Institute of Technology. Professor McHale's talk entitled 'Follow the beat' left the audience inspired. This enjoyable presentation was a perfect conclusion to a great day for the young physiologists.

The YPS social event was held on the same evening, in a stylish restaurant in Dublin city centre.

The standard of presentations, both oral and posters, was outstanding. The oral judging panel of: Stuart Bund, James Jones, Marguerite Clyne and Christine Shortt; and the poster judging panel: Cormac Taylor, John Baugh and Deirdre Edge, had a tough job deciding the winners.

Prizes for the oral and poster presentation were kindly sponsored by The Physiological Society and Sigma.

The winners were:

**Adrianna Teriakidis**  
University of Edinburgh (oral)

**Susan Chalmers**  
University of Strathclyde (oral)

**Michael Lawless**  
University of Birmingham (poster)

**Eric Lucking**  
University College Dublin (poster)

**Sonia Cadima**  
Smooth Muscle Research Centre,  
Dundalk Institute of Technology  
(poster)

I would like to thank all the organising committee for their hard work and energy. In addition, thanks to The Physiological Society, especially Chrissy for all her help and support. We are also very grateful to the judges for taking time out of their busy schedule to help us with YPS. Without all of these efforts the Young Physiologist Symposium, Dublin 2009, would not have been such a great success.

This event would not have been possible without generous support from The Physiological Society and our commercial sponsors: Sarstead, WPI, Sigma, VWR and Merck.

**Karen Griffin**

## The British Science Festival, Guildford, September 2009

This year I attended the British Science Festival with a student bursary sponsored by The Physiological Society. Although the Festival seemed to be primarily aimed at younger children, it had so many events that there was always something interesting going on.

The majority of events were groups of short 30–45 min lectures with a discussion session afterwards. This had the advantage of presenting

multiple viewpoints but I found that each lecture was slightly too short to go into any real detail. On the plus side, it did mean that I could go to lectures on subjects I know nothing about, yet understand and enjoy them. I attended a lecture on antimatter expecting to be baffled; however, by the end I found I was able to pass on information to my family about how many billion years it would actually take to manufacture sufficient anti-hydrogen to make the bomb in Dan Brown's *Angels and Demons* a reality. It was also a great way to explore cutting-edge science – I found out that organic solar panels are being printed in old colour film factories, and that a portable roll-up TV screen is being developed to sell on the market.

I was one of several undergraduates who received a bursary to attend the Festival, and it was great to have a big group of like-minded people my own age to hang out with, eat dinner with and attend lectures with. Accommodation was en-suite and there was a kitchen available if necessary. Also, internet access was provided in public areas of campus.

All in all, the Science Festival was a great experience for finding out about the cutting edge of other topics and for meeting fellow science enthusiasts.

**Freyja Hopper**

Undergraduate Student, University of Oxford

## Undergraduate Prize for Physiology 2009

In the previous issue of *Physiology News*, we included a list of Undergraduate Prize winners. We are now pleased to add one other winner to this list:

**Laura Corns** from University of Leeds

Congratulations to Laura.

## New Council Members



**Stephen  
Bolsover**

### What is your current job(s) title?

I am professor of Cell Physiology at University College London, and Director of Studies for the Biomedical Sciences degrees (Physiology, Pharmacology, Neuroscience and Biomedical Sciences)

### Summarise your career to date

I did my undergraduate degree at Cambridge and stayed there to do a PhD with Robert Meech. I then went to the US for a postdoc with Joel Brown firstly at Stony Brook and then St Louis. I then returned to England with a lectureship at UCL and have remained here ever since. I have worked on various aspects of cell biology and neuroscience, concentrating on axon outgrowth and calcium imaging.

### Which areas of Council or Society activity would you most like to get involved in?

I am most interested in the educational aspects of The Society's work

Occasionally being allowed to get my hands dirty in the lab.

### What is the worst thing about your current position?

The seemingly endless amount of administration and the increasingly difficult financial climate for higher education in general and science in particular.

### What is the biggest issue facing young physiologists today?

Job security. Obtaining major independent grant income in a fiercely competitive arena.

### Why did you stand for Council?

Generally, I wanted to make a contribution to The Society that has supported my activity over many years. Specifically I was nominated to stand for the post of Treasurer.

### Which areas of Council or Society activity would you most like to get involved in?

The role of Treasurer cuts across most areas of Society activity, so there is scope for wide involvement. One of my overall goals is to help ensure that we direct as much income as is financially prudent towards supporting these activities and The Society's charitable objectives.

### What is your favourite(s) saying or quotation (and who said it)?

'If politics is the art of the possible, research is surely the art of the soluble. Both are immensely practical-minded affairs.' Taken from Sir Peter Medawar's celebrated book of essays 'The Art of the Soluble'. More irreverently, I quite like 'Nothing shocks me. I'm a scientist.' (Harrison Ford, as Indiana Jones).

### What is the most important thing life has taught you?

I firmly believe that you have to strike a sensible work-life balance. Science is important, but so are family and friends.

### Which other scientist (living or dead) would you like to have been, and why?

Not sure that I can specify a single scientist, but for someone working in my area, the early 20th century would have been an exciting time as the work of Bayliss & Starling and others ushered in the era of modern endocrinology.



**Rod  
Dimaline**

### What is your current job(s) title?

Professor of Physiology. Head of Department of Physiology, University of Liverpool

### Summarise your career to date

BSc Hons and PhD in Physiology at the University of Liverpool, specializing in gastrointestinal physiology. Trained in peptide chemistry at the Center for Ulcer Research & Education, Los Angeles with J Walsh and J Reeve, 1979-81. Appointed Lecturer in physiology, University of Liverpool 1979. Visiting Associate Research Professor at UCLA 1989, applying molecular biological techniques to physiology, with J Walsh and V Wu. Current research is focused on molecular regulation of gastrointestinal epithelial function.

### What is the best thing about your current position?

Interactions with colleagues, locally, nationally and internationally.

### What is your current job(s) title?

Reader in Respiratory Physiology

### Summarise your career to date

I received my PhD in Physiology from London University in 1994, and following a Wellcome Trust Fellowship at the University of Wisconsin-Madison, USA. I return to the UK in 1997, where I joined Imperial College London to set up the Academic Unit of Sleep and Ventilation with my clinical colleagues at the Royal Brompton Hospital. My research focuses on the interactions between respiratory control and sleep mechanisms that lead to breathing-related sleep disorders, specifically the cardiovascular and cognitive consequences in vulnerable populations, such as older people and those with a failing heart. The group is supported by the Wellcome Trust, British Heart Foundation and National Health Research Institute.

### What is the best thing about your current position?

The ability to carry out translational research, studying physiological mechanisms – then taking our findings and applying them to clinical practice in patient populations.

### What is the worst thing about your current position?

The stress of 'fitting it all in'.

### What is the biggest issue facing young physiologists today?

Making the transition from postdoc to established lecturer post; there is so much emphasis on producing results.

### Why did you stand for Council?

Like many people I have never forgotten my first Physiological Society presentation; 7 slides – 10 min and finishing before the red traffic light. The Society has a splendid history that we treasure, but we also need to think about the future. I think The Society has an important part to play in disseminating our research using new technology. As travel becomes more difficult we must also maintain the quality of our national meetings.

The link between physiological research and clinical medicine is another feature that I want to bring to the Council. I will encourage The Society to promote translational research through collaboration with other medical groups. Sharing expertise is likely to benefit all.

### Which areas of Council or Society activity would you most like to get involved in?

I am a member of the Meetings Committee, and I think this is important because it is the place where Members interact, and where new Members become engaged with The Society.



**Mary  
Morrell**

### What is your favourite(s) saying or quotation (and who said it)?

I think my students would say that my favourite saying is: 'It's all about the data', or 'Clean up the kitchen'!

My quotation is a poem that was found in the purse of a dear friend of mine after she died of cancer:

*If you think you are beaten you are  
If you think you dare not, you don't  
If you'd like to win, but think you can't  
It's almost certain you won't  
If you think you'll lose, you've lost  
For out of the world we find  
Success begins with a fellow's will  
It's all in the state of mind  
If you think you're outclassed, you are  
You've got to think high to rise  
You've got to be sure of yourself  
Before you can even win a prize  
Life's battles don't always go  
To the stronger or the faster man  
But sooner or later the man who wins  
Is the one who thinks he can.*

Anon

### What is the most important thing life has taught you?

Education is a passport to freedom

### Which other scientist (living or dead) would you like to have been, and why?

Dorothy Hodgkin – she had an amazing life, from the time of the double helix to the structure of penicillin, vitamin B12 and insulin, which she combined with her family, travel and politics.



**Michael  
White**

### What is your current job(s) title?

Reader in Exercise Physiology.

### Summarise your career to date

I read Physiology at The University of Leeds from 1974–77. On reflection, I probably played too much cricket and spent too little time in the library. However, I did gain an interest in exercise and environmental physiology (I didn't realise until much later that this was not a traditional element of undergrad physiology courses so I got lucky). After graduation I joined the then ~3 million unemployed, signed on the dole and sponged off my parents in West Cumbria whilst job hunting. After a 3 month stint as a fuse grinder in a local factory I got an interview for a job that to this day I still don't remember applying for, at the MRC Environmental Physiology Unit in London. There I worked with CT Mervyn Davies and Martin Thompson (now Sydney University) on thermoregulation

in exercise and the physiology of ultra-distance running, amongst other things. In 1979, I transferred to MRC External Staff at the University of Nottingham, as Mervyn's Research Officer. We worked for 7 years in the Department of Physiology and Pharmacology, studying human muscle function in relation to ageing, disuse and fatigue. Here I did a part-time PhD. In 1986 Mervyn took the foundation Chair in Sport and Exercise Sciences at the University of Birmingham and I and the group moved there too. In 1991 I was appointed a Lecturer in the School of Sport and Exercise Sciences at Birmingham, then Senior Lecturer and now Reader. I now run a research group which works on human cardiovascular and respiratory control in health and disease states. I became a Member of The Physiological Society in 1991 and am now an Editor of *Experimental Physiology*.

### What is the best thing about your current position?

Right now the best thing is reading the outstanding contributions that have been submitted to *Experimental Physiology* for inclusion in a special Winter Olympics edition of the journal to be published in early 2010 that Stuart Egginton and I have put together.

### What is the worst thing about your current position?

Attending too many university meetings and receiving too many emails which begin 'with apologies for cross posting'.

### What is the biggest issue facing young physiologists today?

Having their work, their worth and so their future employability judged purely on the basis of the £ or \$ signs associated with it.

### Why did you stand for Council?

It seemed like a good idea at the time! I have always been proud to be a Member of The Society and I want to see it flourish. I also want to give something back to a Society which has been good to me.

### Which areas of Council or Society activity would you most like to get involved in?

I'd better say Society Meetings since that is the committee that I am on!

### What is your favourite(s) saying or quotation (and who said it)?

'We haven't got the money so we've got to think!' (Ernest Rutherford)

'If I had all the money I've spent on drink, I'd spend it on – drink' (Sir Henry at Rawlinson End, Viv (Bonzo Dog Doo-Dah band) Stanhall's great comic creation.

### What is the most important thing life has taught you?

There are no prizes for hard work!

Or to use a cricketing tale:

'You'll bowl a lot worse than that and take a hatful of wickets, lad'. A back-handed compliment I once received from an ex-pro wicket keeper as we walked off a cricket field together, him having kept to me as I exhausted myself, to no avail, on a very hot day.

I suppose I mean that you have to learn to accept the lucky breaks and the hard knocks and hope that it evens out in the end. Not an easy thing to remember when ranting about referees comments on a grant application which clearly wasn't fully read by the referee!

### Which other scientist (living or dead) would you like to have been, and why?

I admire all polymaths, such as Erasmus Darwin (grandfather of Charles) from my adoptive city of Lichfield. He was a founding member of the Lunar Society which met regularly in the Birmingham area from 1765 until it closed in 1813, a few years after Darwin's death in 1802. The name came from their meeting during the full moon, the light from which aided their lengthy and one suspects slightly wobbly, journey home, after the sumptuous dinner and fine wines which ended the day's proceedings. Darwin and his fellow 'lunatics' made many important scientific discoveries and had great influence in Britain, yet they seemed to enjoy a work-life balance that is impossible today.

## New Affiliate Members



**Federico  
Formenti**

### Current Job

Postdoctoral Research Scientist

### Career sketch

I obtained a degree in Exercise and Sport Science in my hometown Verona, Italy, before studying towards my PhD in human locomotion biomechanics at Manchester Metropolitan University in the UK. My doctoral research involved physiological and biomechanical studies useful to understand the origins and describe the development of cross-country skiing and ice skating as means of locomotion. In 2006, I joined the Human respiratory and exercise physiology group in Oxford as



a postdoctoral visiting research fellow; here I also started my second (and last) doctorate. I currently investigate the role of a protein called hypoxia inducible factor in the regulation of cardiopulmonary physiology and metabolism in humans.

#### Best thing about my current job:?

The fantastic team of my supervisors and colleagues, inspiring stimulating ideas.

#### Worst thing?

...it finishes in August 2010.

#### The biggest issue facing young physiologists today is:

Perhaps carrying on working in a research environment, with research jobs offered decreasing in number.

#### I stood for Council because:

I would like to contribute to the activities of The Physiological Society, and to represent my peers at the Council meetings.

#### Areas of Council/Society activity you hope to get involved in:

I would like to be involved in the activities related to the Scientific Meetings.

#### Favourite saying/quotation:

'Love one another as I have loved you' (Jesus).

#### Most important thing life has taught you:

Speaking a English more good than the other Italians.

#### If you weren't you, which other scientist would you like to have been and why?

My supervisor, because he had the good fortune to work with me! (We Italians are known for our modesty, from our Prime Minister down...)



**Sam Passey**

#### Current Job

Postdoctoral Research Scientist

#### Career sketch

My research career has been quite varied so far. After completing my Biochemistry undergraduate degree at the University of Bristol I went on to do a PhD where I studied the Rho GTPase family of signalling proteins and the actin cytoskeleton in lymphocytes. From there I went on to research B cell differentiation at the London School of Hygiene and Tropical Medicine. I have also worked in industry, both at GlaxoSmithKline for a year during my degree and as a Postdoctoral Cell

Scientist at Syntaxin Ltd. About a year or so ago I entered the world of cardiac physiology at the Bristol Heart Institute, where I am investigating cardioprotection and ischaemia-reperfusion injury.

#### Best thing about my current job:

The variety of being involved simultaneously in both clinical and basic science projects.

#### Worst thing:

The challenge of juggling both clinical and basic science projects.

#### The biggest issue facing young physiologists today is:

Not losing heart and maintaining momentum in their research in the face of ever-increasing competition.

#### I stood for Council because:

As a 'newbie' to physiology research, I want to meet as many people as possible from The Society and contribute to the activities of The Physiological Society.

#### Areas of Council/Society activity I hope to get involved in:

I have taken part in a number of public engagement events and schools science events which I have enjoyed a lot, so I am keen to get involved in Society activities in this area. I am also interested in science writing, and will be contributing to *Physiology News* on a regular basis, and sitting on the Editorial Board.

#### Favourite saying/quotation:

Success is the ability to go from one failure to another with no loss of enthusiasm. (Winston Churchill)

#### Most important thing life has taught you:

Keep smiling and don't give up – tomorrow is a new day.

#### If you weren't you, which other scientist would you like to have been and why?

Professor Mina Bissell (renowned breast cancer researcher at UC Berkeley, California). Mina is a great character, a great scientist and an inspiration to women scientists worldwide, showing that it is possible to overcome almost anything to reach your goals, both in science and in life.

## New staff members



**Marie Allan**

Originally from Suffolk, I moved to Cambridge with my husband, Frank,

over 25 years ago. I have two grown-up sons, who both live and work in London. I studied for a degree in Sociology and History as a mature student at Anglia Ruskin University.

I was employed by Cambridge University Press for 15 years. Initially working in the dictionary department, I then cleared permissions to use materials in publications for learners of English as a foreign language. This involved requesting permission for texts as diverse as newspaper articles, instructions to use baby buggies, lyrics for songs, and menus from fish and chip shops!

I'm currently taking two courses in creative writing, so watch out for my best-selling novel!



**Angela Breslin**

I am the new Education Administrator at The Physiological Society. I studied Genetics and Biochemistry at the University of Wales, Aberystwyth and previously worked as a science teacher at a secondary school. I look forward to working with everyone at The Society.



**Diana Jones**

I am returning to The Society's Publications Office in Cambridge after an absence of 7 years. I joined The Society's staff in 1991 and worked on abstracts and *Proceedings of The Physiological Society* for 12 years; some Members may remember me as the face of 'Abstract Corrections' at Scientific Meetings (as Diana Greenslade) during the 1990s. I left The Society in 2002 in order to devote more time to bringing up my two young children. In recent years I have been working as a freelance proofreader for a variety of journals.

I have now rejoined The Society's Publications Office, and will be working with Emma Ward on *Experimental Physiology* whilst Helen Leedham is on maternity leave.

## Ronald H Cook

1914–2009

Ron Cook, who died on 19 July, started work in the Cambridge Physiological Laboratory in 1948. His original appointment was as a Craftsman but he went on to work as Alan Hodgkin's Instrument Maker then Technical Officer until his retirement in 1987. He was a very small man but a larger than life character. This means that he will be remembered by many physiologists who spent time in the Physiological Laboratory, whether or not working in Alan's lab. In March this year, Ron agreed to be included in the Physiological Society's Oral History Programme so he has left a good record of his many activities.

One of his early interests was in aquaria. This was a lucky coincidence because he was able immediately to introduce cuttlefish (*Sepia*) to Cambridge, where they were used by Alan Hodgkin and Richard Keynes for the ion flux measurements that backed up the then new ionic theory of the action potential. Vintage cars were another particular passion. At the time of his death he had been Treasurer of the Veteran Car Club of Great Britain for 41 years so it was fitting that at his funeral the picture on the front of the Service sheet showed him sitting at the wheel of his 1910 Singer. He was a staunch Churchman with firm views on the rightness of the King James Bible (and the wrongness of other versions). He moved to a neighbouring Church when his own Parish Church stopped using King James. An enthusiastic gardener, in his last months he was still tending his 1.5 acre plot with only minimal help. He had been a keen cross-country skier, particularly in Norway, and was a competitive figure skater. It was a great disappointment to him that the cold spell in February this year ended before any skating championships could be held at Earith. He would certainly have competed, driving himself there and back.

**Ann Silver**

**Peter Stanfield writes:**

I first noticed Ron Cook when I was an undergraduate reading physiology



in Cambridge. From time to time, I would see a diminutive, but highly energetic and rather distinguished figure emerging from the basement of the Physiological Laboratory. I fancied that this might be the legendary Lord Adrian, whom I knew to have an office down there. Later, as Alan Hodgkin's graduate student, I came into contact with Ron on a daily basis. He was outstandingly supportive to someone just at the start of their career and it would be hard to forget – even if I wished to – the kindness and patience shown to someone rather naïve, inexperienced and uncertain. This was at a time when it was sometimes less fashionable for chief technicians to be so directly helpful.

Ron was the scion of a family that had set up a plastering company in Cambridge. A check of the current company web site ([www.georgecook.co.uk](http://www.georgecook.co.uk)) soon dispels the idea that this was a mundane inheritance, though Ron's father worked instead for the University of Cambridge, becoming Assistant Librarian, a position more elevated than its title might suggest. Ron was educated at the Perse School in Cambridge and he earned considerable pocket money during his boyhood, repairing clocks for various shops that advertised their (as it turned out lesser) skills in this craft. Rather than completing his undergraduate education in Cambridge, Ron apprenticed himself to the Electric Master Clock Company, whose owner, Hope Jones, soon recognised and used Ron's talents, but to an extent that led to Ron feeling somewhat put upon. So Ron moved to Pye Ltd, a Cambridge company that was well known in the UK a generation ago as a maker of radio (perhaps I should write wireless)

and television sets. Pye had been set up as a company of instrument makers by father and son, WT and WG Pye. During the Second World War, they were involved in work for the War Department, with Ron working on proximity fuses and in other devices for the RAF.

Ron Cook became Alan Hodgkin's instrument maker in 1948, continuing to work with very considerable distinction until his retirement in 1987. His immediate role was to build the feedback amplifier used in Plymouth later that year in the first voltage clamp experiments on squid axon. He went on, of course, to provide the technical support and the instrument making that formed the infrastructure for experimental work that laid the foundations of modern electrophysiology. As well as building countless amplifiers, with W Nastuk he designed and built the first microelectrode puller. So effective was this puller, compared with commercial pullers available in the early years, that I had one built to Ron's design when I moved to Leicester. The only obvious difference from Ron's construction is in the winding of the solenoid coil – immaculately neat in his, somewhat less tidy in the Leicester model. So far as I know, the Leicester puller is still in use today. Ron built the Perspex model designed and used by Hodgkin and Keynes to mimic their measurements of unidirectional potassium fluxes in squid axon, and this work and the model led directly to the concept of an ion channel as the route for ionic transfer. He made the single fibre chamber used by Hodgkin and Horowicz in their experiments on dissected single muscle fibres; and many more experimental chambers besides. He designed and built an ingenious Faraday cage for Hodgkin's later experiments on retina, where the experimental manipulations could be conducted from outside the cage.

His instruments, experimental chambers and other devices functioned in a state-of-the-art way. But there was also a fine, if slightly old fashioned, aesthetic in what he did. Instruments were built in home-made, but beautifully

crafted metal boxes, with front panels finished in hammer-tone enamel and neatly lettered. Having to make panel-mounting boxes from Lektrokit was one of my many later disappointments in life. Perspex chambers had the cut edges of the plastic polished so perfectly, that it was near-impossible to tell which edges had been cut and which were part of the surface of the original sheet.

Ron also designed, set up and for many years ran the aquarium in the Physiological Laboratory, which provided access, on condition of their humane treatment, to *Sepia*, *Carcinus*, *Maia* and many other rather exotic creatures for a place so far from the sea. This aquarium also housed frogs, used for nerve and muscle research, and terrapins used in work on retina. Some of my earliest sightings were of him in his green apron – rather larger it seemed than he was – which he wore when on aquarium duty.

His other great skill, which came from his long-standing repairing of clocks – even those that others had given up on – was as a great fixer of things. If things didn't work, the matter was put right pretty much immediately. This may seem run of the mill, but it was far from being so, since you were able to take for granted that things would work. Oscilloscopes were kept in correct calibration, their amplifiers and time bases working. Manipulators did not drift. All this was no mean feat, as I was to discover later in other places.

From time to time, Ron would turn up to the Laboratory in his veteran car. In this he looked a little as though he was auditioning for a main part in *The Wind in the Willows*, though his enthusiasm was far from ephemeral and his competence considerable, as always. He had perhaps been inspired to this interest by the film *Genevieve*, with the dream of driving Kay Kendall on the London to Brighton run. Indeed, his car, and he more briefly, appeared in the film *Those Magnificent Men in Their Flying Machines*, though I have never managed to identify him even after several viewings. But he almost fulfilled his dream, and indeed he made up for Alan Hodgkin's earlier

decision to decline a part as an excise man in *Whisky Galore*, offered when the Hodgkin family were on holiday in Barra.

I remember Ron with great affection, a very widespread feeling among people who worked in the Physiological Laboratory during his long service there. Elements in his character were quirky and unexpected – for example, the long-time reader of the *Morning Star*, and the man who took pride in 'never having called anyone sir in my life' belied superficial expectation. In some ways, he was a little like the humane, humorous, ebullient and genuinely kind character in a Dickens novel, who intervenes just at the right minute, completely selflessly and with a surprising lack of fuss to save the book's eponymous hero. Several scientific careers owe him for his generosity, given freely and with wonderfully warm good humour.

### Alan Cattell, Principal Assistant in the Physiological Laboratory, Cambridge writes:

My lasting memory of Mr Cook is of him striding up and down the main stairway, two or three steps at a time, garbed in a green plastic apron that stretched to the floor. In one hand would invariably be a pair of vernier callipers and in the other a piece of equipment or material that he was working on or with. He would rush past saying 'Morning old boy' or calling you Rupert or some other name, but never your own. On occasion he would be puffing on a cigar (which was at that time permissible) and he would leave a trail of smoke as he rushed about his business. At one period he looked after a number of alligators that were being used for a research project and unfortunately was badly bitten by one of them. He was sent off to Addenbrooke's Hospital and explained how he got his injury; he was surprised when no one would believe him.

In the mid-seventies there was a television programme called '*It ain't half hot Mum*' about an army concert party based in India and then Burma. One of the characters was a

diminutive individual who was known as Gunner Sugdon, or Lofty to his friends, and he wore shorts and a pith helmet. One morning Mr Cook arrived for work dressed in sandals, shorts and shirt, all beige, and was greeted with 'Look out chaps here comes Gunner Sugdon'. To that comment Ron responded by marching briskly down the corridor, arms swinging and a broad grin on his face. He did like a joke did Mr Cook.

### Jeffrey T Potts

1958–2009

(Born 26th December 1958 and died 2nd September 2009)

I provide this remembrance of Jeff from the perspective of a mentor and close friend and with the knowledge that his untimely death from the complications of sarcoma cut short the blossoming career of someone destined to be a leader in the field of neurophysiology.

Jeff was born and raised in New Brunswick, Canada and remained proud of his Canadian roots throughout his life. However, once he had experienced the heat and wide open spaces of Texas he longed to return there despite his successful sojourns at the Medical Centers of Johns Hopkins University, Wayne State University and the University of Missouri-Columbia.

Jeff received his Bachelors of Science degree in Physical Education from the University of New Brunswick in 1982 and a Masters of Arts degree in Exercise Science from Indiana State University in Terre Haute, Indiana. In 1986 he entered the PhD program in the Department of Kinesiology at the University of Maryland, but somewhere along the way felt that he wanted more than just an applied science degree. Why he chose to seek to join my research program at the age of 31 and work to obtain a PhD in Biomedical Sciences (Physiology) has always been a mystery to me, especially when I asked that he obtain additional courses in the fundamental sciences before joining me. However, I could not have been more fortunate to have him join my group as he soon began to develop his own research questions and address them with his well-known enthusiasm and insights



into the necessary experiments. Indeed, he developed a new method of using our neck pressure/neck suction technology to examine the carotid arterial baroreflex during dynamic exercise from rest to maximal exercise. His particular work was published in the *American Journal of Physiology* in 1993–1995. However, his development of the ‘built curve’ technique of modelling the carotid baroreflex function has remained a fundamental component of our ability to investigate the arterial baroreflex. After receiving his PhD degree in 1993 he followed his interest in developing his background in computational physiology by joining Artin Shoukas in the Department of Biomedical Engineering at Johns Hopkins University School of Medicine for a post-doctoral fellowship in Biomedical Engineering. His work focused on the role of arterial compliance and venous resistance on the carotid baroreflex control of the circulation and was published in three papers in the *American Journal of Physiology*. Subsequently, he returned to Texas and joined Jere H. Mitchell MD at UT Southwestern Medical Center (UTSWMC) in Dallas. Using a more reductionist approach, he developed a new set of skills by which he could delve deeper into the mechanistic questions of baroreflex control of blood pressure and sympathetic activity during exercise pressor reflex activation. It was during this time (1995–2000) that he published several important papers identifying the neurotransmitters within brainstem medullary centres that are involved in baroreflex and exercise pressor reflex control. Also while in Dallas, he met and collaborated with Julian Paton, which allowed him to investigate these reflexes at a more cellular and molecular level. His collaboration with Julian was, in my opinion, the one that in his eyes solidified his place in neurophysiological circles and the one that confirmed to him that he had achieved a major goal in his life. This collaboration with Julian was ongoing and productive until his death. It is unfortunate that he could not have a longer time to savour his research success and enjoy his life with his wife, Jessica, and newborn daughter, Nadia.

### Peter Raven with Jere Mitchell and Artin Shoukas



Jeff on his day of graduation with his mentor Peter Raven.

### Julian Paton writes:

I first ‘met’ Jeff when with Jere Mitchell he wrote a viewpoint article on a paper we had just published on a spinal somato-sympathetic generator in *The Journal of Physiology* (Chizh *et al.* 1998, *J Physiol* **508**, 907–918). Within their viewpoint article, which was entitled ‘Synchronization of somato-sympathetic outflows during exercise: role for a spinal rhythm generator’ (see Potts & Mitchell, 1998, *J Physiol* **508**, 646) there was a clear appreciation for what we had published and how it correlated well with work from their laboratory. These friendly tones were soon solidified when, for the first time, I met Jeff in person at a Physiological Society meeting in Southampton in 1998 when he was working with Michael Spyer at the Royal Free Hospital. First impressions were a highly charged, serious and motivated scientist who was full of self confidence and on a mission. He knew what he wanted and he had a very clear and focused agenda. Jeff was an exceptional cardiovascular systems’



Jeff enjoying good times in a wine cellar with his mentors Jere Mitchell (left), Peter Raven and Artin Shoukas (right).

physiologist; he had experience of working with both humans (with Peter Raven) and subsequently whole animals *in vivo* (dog, cat and rat with Jere Mitchell and Artin Shoukas).

What followed from the Southampton meeting until his untimely death last month was a most enjoyable 11 year collaboration. We both visited each others laboratories five times each between 1998 and 2007 and spent time together running experiments and then interpreting the data and planning subsequent studies for the following day, usually in a bar or pub. The enjoyment partly came from the science but, importantly, from the extreme fun we had doing the work together. Through the work we developed a close friendship. On two occasions Jeff’s visits coincided with me moving house. Such was Jeff’s generosity he insisted on helping me both times. This was a remarkable gesture of friendship. I could not compete with this but was his best man at his wedding to Jessica 2 years ago.

Jeff was a remarkable athlete who ran most days for around an hour and completed many marathons. This was in itself incredible given the serious motor car crash he had many years earlier. At that time, doctors were not sure he would even walk again. Nevertheless, he was impressively fit and whenever I joined him on a run he was kind enough to jog at half throttle; he was always such a considerate and thoughtful man. Of course, all this running stimulated a favourite pastime of his which was drinking good beer with friends and exercising his sense of humour, something we will all miss.

I am delighted that we were successful with our latest joint publication together. This was accepted in *Circulation Research* shortly after his death and will be dedicated to his life as a scientist.

Our thoughts are with his lovely wife, Jessica, their new daughter Nadia, his parents and his two sisters. Memories of Jeff will of course never die: his characteristic laugh that boomed across any noisy bar, his inability to keep to time with his scientific presentations, and his compulsive and highly focused attitude to his science.



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