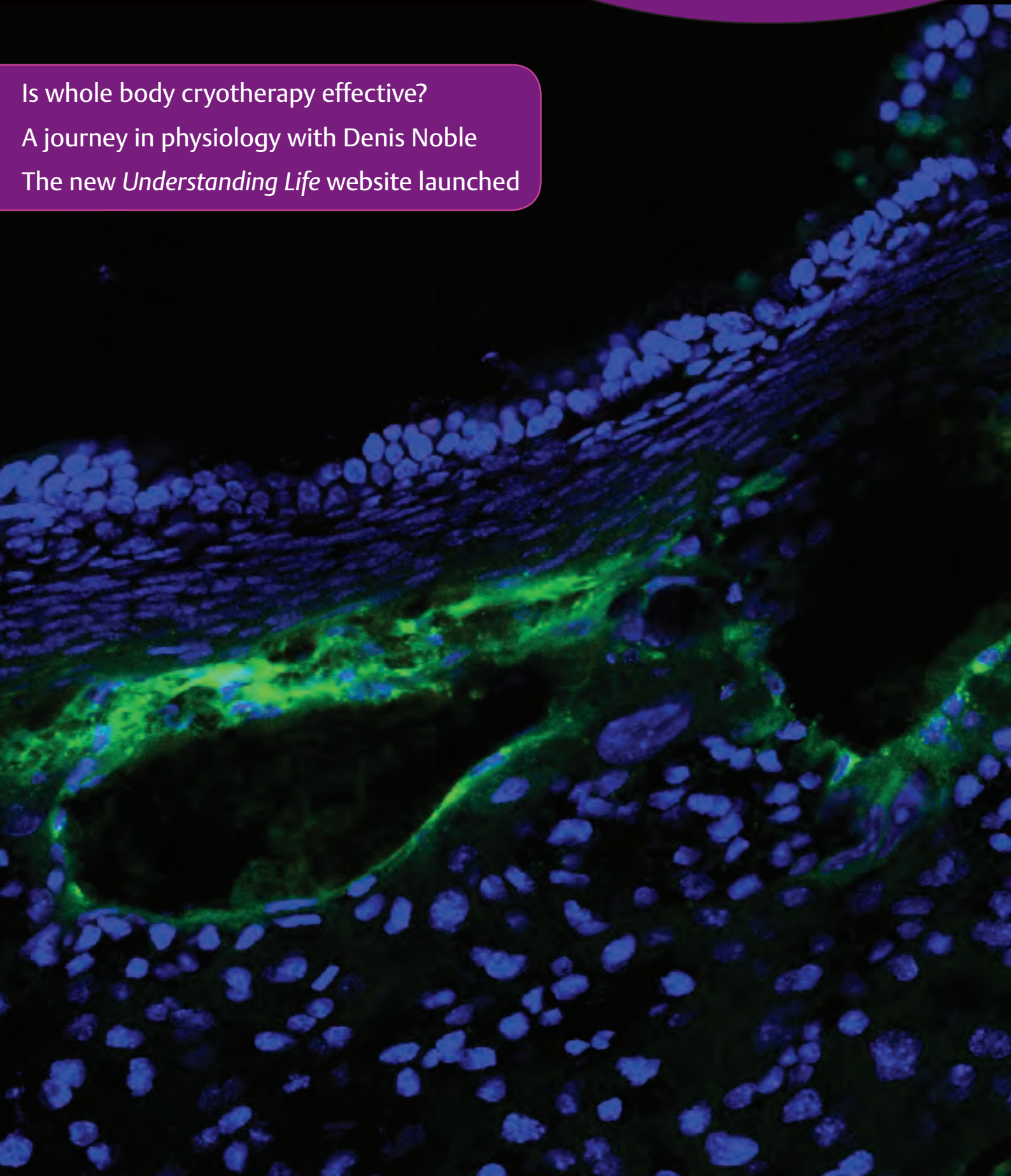
# PHYSIOLOGY NEWS

winter 2011 | number 85

Is whole body cryotherapy effective?

A journey in physiology with Denis Noble

The new *Understanding Life* website launched

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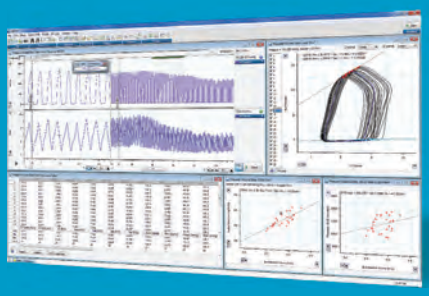

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The Society's dog. 'Rudolf Magnus gave me to Charles Sherrington, who gave me to Henry Dale, who gave me to The Physiological Society in October 1942'

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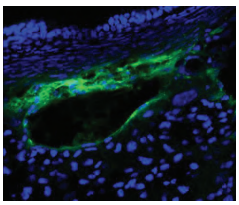
# PHYSIOLOGY NEWS





Cover image: FAM-labelled peptide intravenously injected into a pregnant mouse (p. 50).

# 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

### Membership applications
Applications for membership to The Physiological Society are considered on a rolling basis, and a decision is normally made within 15 working days. For full information, please visit: www.physoc.org/membership

### Is your membership information correct?
Please check and update your details at www.physoc.org, under 'My Physoc Profile'.

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## *Physiology News*

### Deadlines
Letters and articles and all other contributions for inclusion in the Spring 2012 issue, No. 86, should reach the Publications Office (magazine@physoc.org) by **17 January 2012**. 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 Managing Editor or a member of the Editorial Board of *Physiology News* (see contents page for details).

### *Physiology News* online
*Physiology News* online: www.physoc.org

## Guidelines for contributors

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 Managing 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).



## In this issue

Welcome to the Winter 2011 edition of *Physiology News*.

The unravelling of the cellular and molecular basis of membrane excitability and nerve transmission stands as one of the crowning achievements of 20th century physiology. Testament to how far we have come in our understanding can be drawn from many of the News and Views articles on pp. 15–36. We can now even build computer models that simulate complex cellular and multicellular electrical activity – thanks in no small part to the pioneering efforts of Denis Noble, who gives a personal account of some of his work on p. 11 (see also p. 40).

Roger Tsien is a scientific hero of many biologists, including me, so it is a pleasure to have an interview with him in the magazine (p. 9). This dates from his 'flying visit' to Physiology 2010, where he gave a truly memorable Annual Review Prize Lecture.

Plus: our regular mix of features, with reports of upcoming (and previous) meetings, journal and Society news and much more.

We also say goodbye in this issue to two leading figures in human physiology – John Widdecombe and John T Shepherd (Obituaries, pp. 54–56). By rather poignant coincidence, in the last issue we ran a piece that John Widdecombe wrote shortly before his death in late August (*PN* **84** p. 7). Together with his obituary, it hopefully does justice to the life of an outstanding physiologist.

Finally, this is my last issue as Editor, and so my last of these columns. I hope you have enjoyed reading them as much as I have (mostly!) enjoyed writing them.

**Austin Elliott**
Editor

## Letter to the (next) Editor

This editorial marks the last one of my term as Editor of *Physiology News*, as I am bowing out after eight years – not to mention three before that as Deputy Editor, and more before that on the editorial group. My very first meeting of the magazine group in late 1998 (sic) seems rather long ago now.

Under the circumstances, I hope you will forgive me if I use this parting column to have a slightly personal look back over the years in between, and share some thoughts on the challenges of editing, and on what learned society magazines like *Physiology News* do.

Departing editors often like to take a look at the high and low points of their editorship. I will start with the highs.

My best moments as editor have been the days a whole issue appears in the post, especially when we have managed to put one together featuring something a bit special – e.g. the recent one with Bob Edwards' Nobel Prize on the cover and in the pages. Another source of satisfaction is when a new feature we have dreamed up matures into something regular. A big strength of *Physiology News* has always been the collective nature of the Editorial Group, with all members kicking in ideas for features – so much so that I cannot actually remember whose idea recurring features like *Living History* or *Soapbox* originally were. The one feature I will take personal credit for is the *Unbelievable!* satire column, inspired by my lifelong love of the magazine *Private Eye*. Humour is always tricky, since what one reader finds hilarious may be totally lost (or worse) on another. However, I'm glad we took the plunge with the column, which I am pleased to say recently passed its 10th anniversary.

What about worst moments, or greatest disappointments? Probably the greatest fear of any editor is publishing something that is plain, and embarrassingly, wrong. Controversy is fine – and indeed often a good thing – but no editor likes to be seen to have made a flagrant and public error of fact. I have been fortunate that we have not really had a major error of this type during my editorship (touches wood). However, such problems are, by the nature of magazine publishing, a matter of 'when rather than if' – prospective and future editors take note. To give a small personal example, one of the very first paragraphs I ever wrote for the magazine, years before I became editor, concerned Dr Jonathan Miller, who had mentioned in a BBC radio interview that he sometimes wished he had spent his career 'doing physiological research with Adrian... publishing it in *J Physiol*'. Unfortunately, the paragraph I wrote about this mixed up the two Adrians (father and son). Several senior Members of The Society promptly wrote in to put me right, thus offering another lesson to prospective editors – far more people will comment when you do something wrong than when you are doing something right.

The most nerve-racking editorial moments typically involve a looming print deadline, together with an article that may need a lot of revision, or that may be questionable to run. Again, there have been gratifyingly few of these – largely due to the excellent organizational skills of the Executive Editors I have worked with – and we have only ever 'pulled' one article in all my time at *Physiology News*. One piece of recent editing that sticks in the memory was the article in PN 82 by medical research whistleblower Dr Peter Wilmshurst. He was being sued for libel at the time by an American medical device manufacturer that had shown great enthusiasm for firing off writs and legal letters. At such times there is inevitably the potential for tension between magazine editors (who typically want to put out material on topical, and even controversial, subjects) and proprietors who are understandably jumpy about the possibility of being sued. Which reminds me that, as scientists, we should still be pushing for a robust public interest defence of comments on topics of scientific interest – so do please visit the *Campaign for Libel Reform* website.

The main disappointments editors have relate, I think, to the comparative lack of responses and feedback. All editors, without exception, would like to see more letters to the editor, and more debate, in their pages. Perhaps online response threads are the way to do this, but even then the debate depends upon readers' – your – willingness to take the time to comment.

Finally, some words on the subject of learned society magazines. *Physiology News* is now a comparative rarity amongst such publications in being written and edited by working scientists – 'by scientists, for scientists'. This was more common ten or fifteen years ago, but many societies have switched to set-ups where their magazines are largely run by freelance science journalists or editors.

There can be positive reasons for this, including the desire to make content more thematic, or more uniform in style, or consciously to address a wider community than just scientists. However, I suspect that an equally big driver has been the increasing pressure on scientists' time. In the modern world, most employers might wonder why a scientist is writing, or editing, something that does not have a PubMed listing or an Impact Factor. Speaking as an editor, I can see arguments for and against the more 'professional' paid set-ups. However, I personally think 'by scientists, for scientists' remains something of real value – and increasing scarcity – and thus worth preserving.

It is also worth considering the many implications for magazines of the explosion in online science communication over the last decade. To my mind, a key one of these is that people both in, and beyond, the academic community are often frustrated with misleading science messages in the mainstream media. In internet-based science communication, especially via blogs, it is the direct communication from scientists themselves, with its promise of a view unvarnished by spin and PR, that draws the audience. What readers seek, in other words, is 'authenticity' and an identifiable authorial voice. Though learned society magazines are not directed at the public, I would certainly hope 'authenticity' is a word that would describe *Physiology News*; it is certainly a word most editors would cherish. If readers think what we have done with *Physiology News* over the last dozen years has met the various challenges of being 'informative' 'readable' 'interesting' and 'authentic', then I will retire a happy (ex)editor.

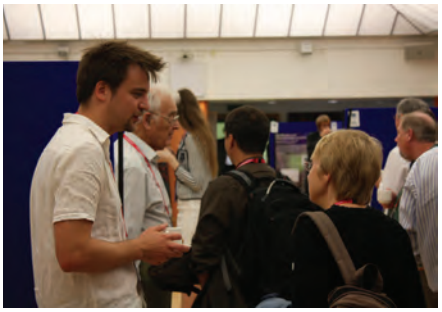
**Austin Elliott**

# Epithelial & Membrane Transport Themed Meeting, UCL 1–3 September 2011

Walking around my department one day this summer, I noticed a poster advert for The Physiological Society Meeting. Clearly word had gone out to every corner of academia, including the notice board by the loos, and I realised I'd have to be there. So I immediately set about penning a long entreating email to Sarah Bundock asking to be allowed to attend this hallowed event, despite the closing date having passed many moons ago. To their credit, Sarah and her team sorted everything out with the minimum of fuss, and so bright and early one morning I found myself fighting through the London commuter throng to get to the Royal Free Hospital.

I scored my first own goal when I realised that the smartly dressed gentleman I'd rudely pushed in front of on my way in turned out to be not only one of the speakers, but fellow *Drosophila* biologist Subrata Tripathi. I compounded this error when I realised that the professorial looking chap I'd been 'buttering up' with my best science chat was in fact at the hospital for an operation. Deciding that scientific networking wasn't perhaps my forte, I grabbed my programme, a refreshing coffee and – after stealing a large handful of sweets from the Stratech exhibitor's stand – settled in to be educated about epithelial and membrane transport, a field somewhat distant from my speciality in Huntington's disease, but which my recent research had been encroaching upon.

Given my limited background knowledge, I was pathetically grateful that Martin Konrad's talk that kicked off the conference included some great slides explaining the basics of tight cell junctions and transepithelial transport. From then it was on to David Shirely's disease structure/function session, where a series of talks by Detlef Bockenhauer, Anselm Zdebik and Marc Paulais illustrated how epilepsy, ataxia, sensorineural deafness and salt-wasting renal tubulopathy could all be associated with a channelopathy. The sheer variety of symptoms associated with transport disorders was very interesting, and later in the Plenary Lecture Jonathan Ashmore explained in much greater detail advances in understanding how transport defects within the complex structure of the ear lead to deafness.



In my haste to be punctual I had left my own poster in my room that morning. Therefore I had plenty of time to examine other posters on display, which covered a huge range of topics. The wine was plentiful, the beer was cold, and whilst I didn't attend The Society dinner following the poster session, the sight of senior Society Members looking slightly the worse for wear the next morning led me to deduce it had been a great success.

The Friday session held the unusual distinction amongst conferences of actually running to schedule – despite all the speakers turning up – so congratulations to all the speakers, competing as they were with sunny weather and close proximity to Hampstead Heath. The afternoon poster session again afforded ample opportunities for networking to all – all except for the unfortunate Julian Dow, whom I'd spied walking in and proceeded to bombard with enthusiastic *Drosophila* shop talk for almost the entire hour-and-a-half session, after which he acquiesced to working together on a metabolomics project rather than face any more of my chat!

So overall the meeting did exactly what it should: novel results were presented, new ideas discussed, new collaborations initiated and, of course, quality catering provided. Also – as a newbie to The Society – it was particularly noteworthy to see how professional all The Society leaflets, posters and handouts looked, and how smoothly the whole Meeting was run.

**Edward Green**
University of Leicester

# IUPS 2013 – Symposium proposals are now being accepted in the following subject areas

IUPS 2013
21–26 July 2013 Birmingham, UK

- Ageing
- Biomechanics (General & Comparative)
- Blood
- Cardiac Physiology
- Cardiovascular, Respiratory & Autonomic Control
- Cell Neurophysiology
- Cell Signalling
- Clinical & Translational
- Comparative & Environmental Physiology
- Conservation Physiology
- Development & Plasticity
- Ecological Physiology
- Endocrinology & Neuroendocrinology
- Epithelia & Membrane Transport
- Ethical issues in Physiology
- Evolutionary Physiology
- GI & Liver
- Human Physiology & Exercise
- Integrative Neurophysiology
- Ion Channels
- Locomotion
- Microcirculation
- Muscle & Motility
- Placenta & Perinatal Physiology
- Renal Physiology
- Respiratory Physiology
- Sensory Functions
- Smooth Muscle
- Somatosensory Physiology
- Systems Biology
- Teaching/Education
- Vascular Biology
- Water & Electrolyte

**Submit online at www.iups2013.org**

# Themed Meetings

Applications to host 2013 Themed Meetings are now open

We are now seeking applications for Themed Meetings in the areas of Epithelia & Membrane Transport and Vascular & Smooth Muscle Physiology, which will take place in December 2013

To apply, visit **www.surveymonkey.com/s/TM2012**
The deadline for applications is **29 February 2012**

For an informal discussion about a potential proposal, please contact Nick Boross-Toby at **meetings@physoc.org**

The Physiological Society

# The Biomedical Basis of Elite Performance

The Physiological Society and the British Pharmacological Society (in association with John Wiley & Sons, appointed by The London Organising Committee of the Olympic Games and Paralympic Games as a licensee to produce official London 2012 books), are organising a 3-day international conference at The Queen Elizabeth II Conference Centre in central London from 19 to 21 March 2012.

This premier sports medicine and science meeting will bring together leading researchers to address the overarching theme of the Biomedical Basis of Elite Performance.

The meeting is divided into seven sessions where invited speakers and short oral communications will provide latest research findings along with other important recent developments.

- Cardiac, respiratory and vascular aspects of performance
- Drugs in sport
- Neuromuscular function, muscle phenotype and mass regulation
- Exercise metabolism
- Thermoregulation
- Genomics and exercise
- Sport and exercise medicine

Specialists and non-specialists are invited to attend and engage in what will no doubt be a programme of lively discussions.

The meeting will be complemented not only by short oral communications selected from submissions but also by related poster communications and a social programme.

Each day will conclude with one of the following plenary presentations:

- *The biological basis for exercise and health* – Frank Booth (University of Missouri, USA)

- *How science and medicine has changed how athletes train and perform* – Scott Drawer / Christian Cook (UK Sport, UK)
- *A life-time contribution to our understanding of the elite athlete* – Bengt Saltin (University Hospital Copenhagen, Denmark)

The meeting will also feature the *Bayliss–Starling Prize Lecture* by Jerome A. Dempsey (University of Wisconsin-Madison, USA) and the presentations and judging of The Society's schools competition education event '*The science of sport: How to win gold*'.

Abstracts from the Meeting will be published in one virtual edition and will be available as part of the registration package to all delegates in advance of the event. *The Journal of Physiology*, *Experimental Physiology*, *British Journal of Pharmacology* and *The Scandinavian Journal of Medicine and Science in Sports* (all published by John Wiley & Sons) will all be publishing selected abstracts.

Registration is now open and available at the reduced rate of £75 before the early booking deadline expiry(19 February 2012).

There are a number of Young Physiologists' Bursaries available – apply before 15 January 2012 for up to £200 to support your attendance.

Abstract submission will close on 15 January 2012.

The programme, abstract submission and registration are available now at the official website:
www.bbep2012.org

**Invited speakers:**
Daniel J Green
Liverpool John Moores University, UK
Benjamin Levine
University of Texas Southwestern Medical Center, USA
Markus Amann
University of Utah, USA
Douglas Seals
University of Colorado, USA
Daniel Theisen
CRP Santé, Luxembourg
Carsten Lundby
University of Zurich, Switzerland
David Cowan
King's College London, UK
Fawzi Kadi
Örebro University, Sweden
Martial Saugy
Centre Hosp. Univ. Vaudois, Lausanne, Switzerland
Simon Gandevia
Neurosci. Res. Australia and UNSW, Sydney, Australia
Peter Zammit
King's College London, UK
Stefano Schiaffino
Università degli Studi di Padova, Italy
Jan Lexell
Lund University Hospital, Sweden
Marco Narici
Manchester Metropolitan University, UK
Phil Atherton
University of Nottingham, UK
Bente Kiens
University of Copenhagen, Denmark
Erik Richter
University of Copenhagen, Denmark
Marty Gibala
McMaster University, Canada
José González-Alonso
Brunel University, UK
Mike Sawka
Army Research Institute of Environmental Medicine, USA
Lars Nybo
University of Copenhagen, Denmark
Claude Bouchard
Pennington Biomedical Research Center, USA
Jamie A Timmons
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Steven Blair
University of South Carolina, USA
Magnus Karlsson
Lund University, Sweden
Michael Kjær
University of Copenhagen, Denmark
Peter Magnusson
University of Copenhagen, Denmark

# The Biomedical Basis of Elite Performance

19–21 March 2012

The Queen Elizabeth II Conference Centre London

- Cardiac, respiratory and vascular aspects of performance
- Neuromuscular function, muscle phenotype and mass regulation
- Genomics and exercise
- Exercise metabolism
- Sports and exercise medicine
- Thermoregulation
- Drugs in sport

**www.bbep2012.org**

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The Physiological Society

# Physiology 2012
2–5 July
Edinburgh International
Conference Centre
United Kingdom

## Key dates

Registration opens 1 January 2012

Abstract submission opens 1 March 2012

## Prize lecturers

Cori Bargmann – Rockefeller University, New York, USA

Gareth Leng – University of Edinburgh, UK

Diane Lipscombe – Brown University, Providence, USA

Jere Mitchell – UT Southwestern Medical Center, Dallas, USA

Peter Ratcliffe – University of Oxford, UK

Holly Shiels – University of Manchester, UK

www.physiology2012.org

The Physiological Society

# What makes a Nobel Laureate tick?

In July 2010 Roger Tsien, Nobel Laureate, arrived in Manchester to deliver The Society's Annual Review Prize Lecture at Physiology 2010. Ian Forsythe and Brian Robertson were his 'minders' on that day. Here they share their impressions.

We were slightly tense as we waited in a hot, dingy, crowded Terminal 1 at Manchester Airport. The afternoon flight from Zurich was on time and we had an appointment to pick up Roger Tsien, Nobel Laureate. Roger has a predictably busy international schedule and was to be in Manchester for less than 24 hours, so we were delighted that he had agreed to talk to us. It was a little surreal waiting at the Arrivals gate and watching returning Mancunian holidaymakers in sandals, occasional sombreros and shorts trailing cases and children. Roger Tsien finally emerged with much more decorum and on the drive back to Manchester we chatted about his first visit to the UK and his impressions as a graduate student in the early 70s.

**Ian Forsythe and Brian Robertson**
**(Q):** So Roger, where did you graduate?

**Roger Tsien (RT):** It's a tough choice for a third son, especially when your elder brothers set such a high bar... both went to MIT.

So Roger chose Harvard... where he dabbled in early molecular biology, quantum mechanics, oceanography and avoided organic chemistry! But what got him inspired were the neurophysiology courses from Hubel, Wiesel and John Nicolls, which triggered an enduring fascination with the mind and brain.

**Q:** Why did you come to Cambridge for your PhD?

**RT:** Well my brother Richard had been a Rhodes Scholar in Oxford, but that required some sporting prowess and I was a reluctant athlete... However, there was a Marshall Scholarship at Cambridge so I applied and in 1972 the Marshall Commission wrote back to say they had allocated me RH Adrian as my supervisor. I had no idea who this guy was, so I asked Dick (Richard Tsien, the eminent cellular

Roger Tsien

electrophysiologist and Roger's older brother) and he said he worked on skeletal muscle – not the brain! I remember commenting to Dick that it seemed a bit of a backwater. Still, I decided to go and turned up in England that October. Sitting down to college dinner one day, someone sat opposite and said "So you are Richard Tsien" (with the correct pronunciation, suggesting he knew my brother) and then to my horror "and you consider muscle physiology a backwater?" Despite this inauspicious start, Lord Adrian was very supportive. I was introduced to the neurophysiology of the day and it worked out well. Later, I found out that my brother had met him at a conference and set me up with those naive comments.

I found I had much more sympathy with the preparation rather than the experiment – *in vivo* experiments were not for me. I wanted a technique that would show activity in multitudes of neurons – not testing one at a time under less than ideal circumstances. A particular luxury of the time was being allowed to develop my own approach. Around a year later I had the chance to talk with Andrew Huxley at a Physiological Society dinner (a somewhat smaller affair than the present day). I'd wanted to discuss some ideas I had for measuring axonal conduction velocities. He had a reputation for testing the mettle of the students, but he'd mellowed by the time the port had been passed (and finished) and we talked on the way home from St John's College. He liked my ideas but I particularly remember his parting shot: "By the way, are you planning to do any experiments during your PhD?" Well, my PhD was not conventional and perhaps I wasn't a good example of a PhD student. I do remember a few acerbic comments. For example, Ann Warner wanted to know "When, Roger, will you choose a preparation?" and a young Andrew Crawford also wondered when I'd "become a proper physiologist?"

**Q:** Perhaps that's the point – you have certainly taken an unconventional approach to all of your research. Given your family connections, perhaps you should have labelled yourself a Physiological Engineer?

By now we had arrived at the hotel, Roger booked in and headed to his room – and back again to get another one as his allocated room was in a windowless basement – no special treatment for Nobel Laureates. We reconvened in the bar and ordered lunch. Having eaten on the plane, Roger was fine with a pot of tea.

**Q:** So what were your PhD projects?

**RT:** I'd started four projects for my PhD: (1) making a fluorescent derivative of tetrodotoxin; (2) attempting to develop voltage-sensitive dyes to follow action potential firing in populations of neurons; (3) fast calcium buffering with BAPTA; and (4) the related development of calcium-sensitive fluorescent molecules, which was what really took off... albeit slowly at first. This problem seemed like the easier one to crack, being essentially chemistry and water. But if I can return to membrane potential probes and get somewhere with that project before I die, I will feel a sense of accomplishment.


Ian Forsythe (left) and Brian Robertson

**Q:** Your fascination with biological fluorochromes and the re-engineering of green fluorescent protein (GFP) to give a broader and brighter spectrum is what has earned you the Nobel Prize...and the rest is history. Will that be a continuing interest?

**RT:** I'm getting out of fluorescent proteins. I have no wish to compete with the young enthusiastic postdocs any more – they have the energy and plenty of ability. The Prize is a great way of tying a ribbon on top of that, then leaving it behind and moving on.

**Q:** Tell us a little about your life – what was your first experiment?

**RT:** When I was young, about 4 or 5, I was at a beach on the East coast. It was a pebbly beach, which hurt my feet. I built a strip of sand to make a painless path cross the pebbles.

**Q:** So if we had to imagine that you couldn't have pursued a scientific career, what would you have done?

**RT:** I'd have been a musician – although I was always not good enough. I still play piano for 10–15 minutes a day for relaxation. I'm good enough to enjoy it and it stops me thinking about science and experiments. In fact, in early 1972 I spent several months in France at a music school before coming to the UK.

**Q:** What's the best scientific advice you ever had?

**RT:** From one of my former Chairmen: "Follow your gut feeling and do what *you* like, rather than what others would like you to do".

**Q:** What advice would you give to a young scientist?

**RT:** Never sink to anything, always jump at everything. Look for an important problem with the highest potential to work and with the least amount of personal pain. The problem needs to be something that brings you joy – daily. And when faced with a choice, take the path that others would not choose.

**Q:** So will the next generation of Tsiens continue with science?

**RT:** I met my wife in Cambridge, and have three children. They have a broad range of interests but there's not a scientist among them; there's a graphic designer, an African Aid worker and my idealist youngest, who would like to teach. I too am the youngest and the eldest has a powerful influence – they are the natural leader; and with Dick in front of me, I needed some powerful drive.

**Q:** Are you optimistic about funding and your future trajectory?

**RT:** Yes. To get funding comes down to whom has got the capability to push it through. More of what we now do has commercial applications, so money is still needed. My research is now focusing on clinical imaging using non-genetic probes, since these will be applicable to humans... and you'll hear more about that at my lecture *(Roger gave The Society's Annual Review Prize Lecture that evening*).

From the Palace Hotel it was a short stroll to the Manchester Art Gallery. Roger had a few hours to kill before his lecture and wanted to visit. Grateful for the untypical Manchester weather, we parted to search for other spectral distractions. In the evening he delighted The Physiological Society with his Annual Review Prize Lecture 'Breeding and Building Molecules to Spy on Cells and Tumors'.

*The 2008 Nobel Prize in Chemistry was awarded to Roger Y. Tsien, Osamu Shimomura and Martin Chalfie for the discovery and development of the green fluorescent protein (GFP).*

## Short Courses in Integrative Pharmacology and Physiology

BPS BRITISH PHARMACOLOGICAL SOCIETY Today's science, tomorrow's medicines

The Physiological Society

Applications are now open for the 2012 *Short Courses in Integrative Pharmacology and Physiology*, which are provided jointly by The Physiological Society and British Pharmacological Society.

These courses are designed primarily for undergraduates wishing to gain hands-on experience of mammalian *in vivo* research techniques. Postgraduates without experience are also eligible to apply.

The courses are run by each of three universities (King's College London, the University of Bristol and the University of Glasgow) and held in two parts. The first part involves the students attending a Home Office training course during the Easter vacation. In the summer, students then attend a five-day hands-on experimental course.

All applications must be collated, assessed and submitted by a suitable representative at each institution. This could be a supervisor, Academic Co-ordinator or Head of Department/School/College (or an individual nominated by one of these).

Applications must be submitted to highereducation@physoc.org by **Monday 5 December 2011**.

For more details, please visit the Education section at www.physoc.org

# A journey in physiology

Where inspiration and experiment led on the road to a mathematical model of the heart

## Introduction: The journey related

A few months ago, I was surprised by a request from Imperial College Press to reprint some of my scientific papers. My puzzlement – after all, everyone can view those papers on the internet – turned to enthusiasm when I found that I was also expected to write some introductory remarks. For the next six weeks my computer keyboard rapidly flowed with its staccato-like clicking as my typing could not keep up with my ideas. Instead of the 'few pages' of remarks, I delivered 150 pages of what can only be described as a book in its own right. It has become Part 1, with Part 2 being the relevant reprinted papers of the combined book (Noble *et al.* 2012). It relates a journey through the many controversies and excitements of my scientific life. Those who have read it before publication, including many of those who feature prominently in the stories, find that it captures some of the cut and thrust of scientific debate and discovery. Controversies date, so they need to be recorded. Those who come later, when the controversies have become history and the discoveries may seem obvious, may not realize how difficult the journey was to establish each milestone in scientific advance.

## The journey begins in UCL

So how did it come about that I had such a story to tell? I feel extremely lucky in many respects. Although initially I opted as a student to study medicine at UCL, my school records showed a clear aptitude for mathematics. Even as an undergraduate in 1957/8 I tried to read the Hodgkin–Huxley 1952 papers (1952*a*,*b*,*c*,*d*; Hodgkin *et al*. 1952) – all 126 pages of them. (Incidentally, how would such work get published today? Would those five papers, one of them 44 pages long, have to be artificially broken up into 12 short papers to increase citation statistics?)

At that stage in my career, I certainly couldn't understand all I read but I did understand that they had created a ground-breaking paradigm. Physiology could be as quantitative and mathematical as physics and engineering. When offered the opportunity to do an intercalated BSc and to be taught by Leonard Bayliss (physical chemistry), Hugh Davson (general physiology) and Bernard Katz (biophysics) I jumped at the opportunity. I can still hear Bayliss' chuckle as he explained Maxwell's Demon, Davson's reply to the question why he didn't give more lectures ('its all in my books!') and the guttural voice of Katz as he showed us how to use complex electrophysiological apparatus. Of course, I asked him about the Hodgkin–Huxley papers since he was also involved in the early stages of the sodium theory (Hodgkin & Katz, 1949) and he was a co-author on the first of the phenomenal set of 1952 papers (Hodgkin *et al.* 1952). He replied that he wasn't sure that he entirely understood them either! I didn't believe him of course.

Lindor Brown (later my head of department at Oxford), John Gray (later to direct the Medical Research Council), Doug Wilkie (muscle mechanics, also one of the first biologists to use computers), Jim Pascoe (the mainstay of UCL physiology for so many years) and Otto Hutter (later Regius Professor at Glasgow) also enlightened us. So much so that the idea of qualifying as a doctor receded into the far distance. At the age of 75 I have still to knock on the door of UCH Medical School and ask to start my clinical course! The decision to delay clinical studies was confirmed by being offered the Bayliss–Starling Scholarship to work for a PhD. Otto Hutter became my supervisor.

## First experimental results with Otto Hutter

He was working on anions in skeletal muscle and the first full paper we published showed that as much as two-thirds of the resting conductance is anionic (Hutter & Noble, 1960*a*). Was this also true of the heart? We found just the reverse (Hutter & Noble, 1961). The great majority of the resting conductance is cationic. It was natural therefore that our next focus should be the cation currents and potassium in particular since Weidmann had already shown that the resting potential of heart muscle follows the potassium electrochemical potential over a wide range of concentrations (Weidmann, 1956). It was also likely, given Hodgkin and Huxley's work on nerve, that delayed potassium currents should be involved in repolarization.


Denis Noble and Otto Hutter on the boat trip down the Clyde at the 1993 IUPS Congress in Glasgow.

We chose sheep and dog Purkinje fibres to work on. The sheep hearts were obtained very early in the morning from a slaughterhouse, or sometimes from RC Garry who was working on sheep fetal physiology at St Mary's Hospital Medical School. We dissected out sections of the fibres, and after recovery we penetrated them with two microelectrodes, one for injecting current pulses, the other for recording the consequent voltage changes. To ensure that most of the current was carried by potassium ions we removed 90% of the sodium in the bathing solution. It was impossible to remove more than this without irreversibly damaging the fibres. We now know the reason for this. The sodium gradient is used by the sodium–calcium exchanger to pump calcium out of the cells. If the sodium gradient is too weak the cells go into calcium overload. The sodium–calcium exchanger in the heart was not discovered until 1969 (Reuter & Seitz, 1969) so we did not know this in 1960. We simply knew that it was impossible to remove all the sodium ions.

The results were exciting because, in addition to the slow onset of $K^+$ current that we expected to generate repolarization, we found that the resting $K^+$ current was carried by an inward rectifier, $i_{K1}$, that closed on depolarization (Hutter & Noble, 1960*b*; Hall *et al.* 1963; Noble, 1965). We had already found such a channel in skeletal muscle (see also Katz, 1949; Hodgkin & Horowicz, 1959) and Edward Carmeliet discovered it at the same time as us in the heart (Carmeliet, 1961).

So, cardiac potassium currents are not like those in nerve. The reason that discovery was exciting is that something has to be responsible for the enormous differences in action potential shape and duration in the two excitable cells. The cardiac action potential lasts hundreds of times longer than that in nerve. There is also rhythmic activity in the heart that must be explained, and Huxley (1959) had just shown that rhythmic activity is inherent in the Hodgkin–Huxley equations. Could the differences we had found in the potassium currents explain these facts?

## First computations

That kind of question requires a quantitative answer. My thoughts turned back therefore to the Hodgkin–Huxley equations and my enthusiasm for their approach was revived. The question I had in mind was audacious to say the least. I doubt whether I had understood more than half of what they had written. And my mathematics was as rusty as you would expect from not having used it for 8 years. I only had an O-level in the subject, and crucially that did not include differential and integral calculus.

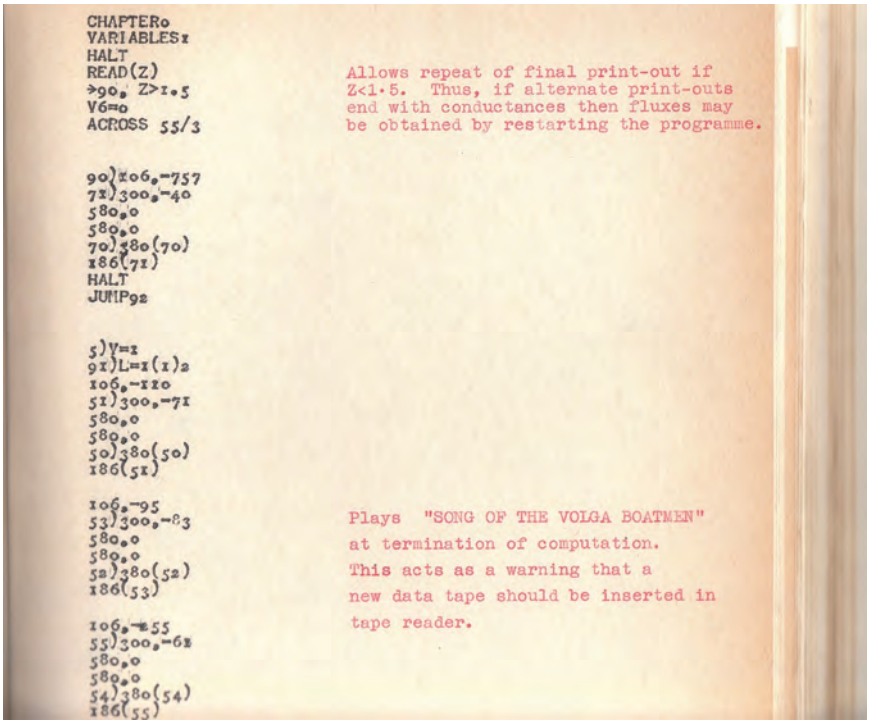


**Figure 1.** Section of the coding of the Ferranti valve computer *Mercury* showing the machine code used at that time. Structured languages like Fortran and Pascal were not yet invented (from Denis Noble's PhD thesis 1961).

Other than the excitement of the chase after a good theoretical explanation of a major physiological property, I still do not know what enabled me to carry the project through. I knew enough to know that I needed to formulate equations based on the experimental results. I also knew that these would need integrating using numerical methods for solving differential equations. So, I went to the only person in the department who was known to have used the extremely rare machines that were called computers in those days: Doug Wilkie. Wilkie had inspired me with his teaching of muscle mechanics, but he must have despaired of the graduate student who now came to him for advice. He judged (correctly) that my mathematical knowledge was insufficient and told me that I would do better to send my results to Andrew Huxley in Cambridge.

I walked away from that discussion crestfallen. I was determined to do the work myself, not to hand it over to someone else, however distinguished. Hodgkin and Huxley were gods in my pantheon, but even a god should not be supplicated with everything on a platter! In a fired-up state I signed myself on for the maths lectures given to the engineers, and I pestered the new 'priests' of technology, the computer scientists, for permission to use one of the earliest valve computers, the Ferranti *Mercury* (Fig. 1). It had been installed, at vast expense, in a basement of one of the Georgian squares near UCL and it was the only machine of its kind in the whole of London.

I must have been very insistent because, eventually, I was given a daily two hour slot on the machine. It was the time no-one else wanted: from 2 to 4 in the morning. I must have worked night and day for weeks on end because later in 1960 I had developed equations and written the machine-code programs that worked. They gave the long and characteristic shape of the Purkinje fibre action potential and, as a bonus, they also generated heart rhythm (Noble, 1960*a*,*b*, 1962) (Fig. 2). A year later, 1961, Alan Hodgkin examined my thesis. The first question he asked was 'Why does the first sentence of your thesis contain an un-referred 'it'?' I am still not at all bothered by an un-referred 'it'. 'It' doesn't matter. I knew I had passed!

## The journey continued: the move to Oxford

In 1963, after lecturing for two years at UCL, I moved to Oxford to set up the first cardiac laboratory there since Burdon-Sanderson was the professor, and published his work showing the long duration of the cardiac action potential in 1883 (Burdon-Sanderson & Page, 1883). The 'Journey of Enlightenment' that had its beginnings at UCL rapidly expanded into new territory as I interacted with the formidable school of Oxford philosophers – most particularly Anthony Kenny, Alan Montefiore and Charles Taylor in those early days – and with those like William Hamilton and Richard Dawkins who were developing the central ideas of 20th century biology around the gene-centric concepts of neo-darwinism.

I examined Dawkins' thesis, done under the Nobel-prize winning Niko Tinbergen. I think the university must have had difficulty finding biologists with sufficient mathematical skill to examine his work. I also organized one of the early debates on *The Selfish Gene* when it was first published in 1976 (Dawkins, 1976, 2006). Readers of *The Music of Life* (Noble, 2006) will know that, although I have interacted with Dawkins, most recently in a debate on evolution published on the website (www.VoicesfromOxford.org), I hold a very different view of biology from him, and I have explained the reasons in some detail in a recent article in *The Journal of Physiology* (Noble, 2011*c*). The metaphors for biological ideas that were used for 20th century biology posed serious problems for physiology since they relegated physiology to the role of understanding the 'lumbering robot', not genetic evolution. Furthermore, those metaphors, such as the 'selfish gene' itself, now form an outdated view of the relations between genes and phenotypes (Noble, 2011*b*). The view of the 21st century (see, for example, Pigliucci & Müller, 2010; Gissis & Jablonka, 2011; Shapiro, 2011) makes physiology much more relevant to the central questions of biology since we now understand much better how the genome is sensitive to the organism and its environment.

Those interactions with the philosophers and evolutionary biologists in Oxford created the context in which the journey could develop into a book like *The Music of Life*. It is a deeply philosophical book, although written at a popular level. It turns many of the 20th century views of biology upside down and it shows why we need the discipline of philosophy as well as our science. Poincaré (1902, 1968) expressed it well when he said that the worst philosophical mistakes are made by those who think they don't need philosophy. The gene-centric mistakes of the last century were primarily philosophical, not scientific, mistakes (Noble, 2011*c*).

## The Journey: fact or fiction?

A rather different and longer version of this story can be found in chapter 1 of *The Selected Papers of Denis Noble, CBE FRS. A Journey in Physiology Towards Enlightenment* (Noble *et al.* 2012). The sequels can

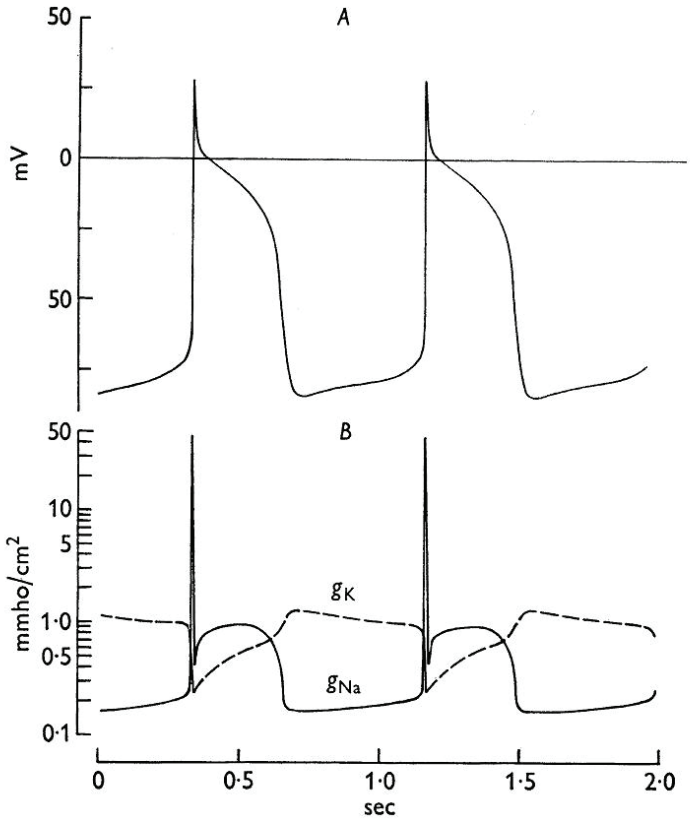


**Figure 2.** *A*, the membrane potential changes. *B*, sodium and potassium conductance changes generated by the 1962 model (from Noble, 1962). Since that time, many additional electrogenic processes have been found and added to computer models of cardiac cells but the broad outlines of the changes in sodium and potassium conductances revealed by this model are still correct.

be found in chapters 2–9 of that book. The 'journey' was much longer than that related here and had many surprising turns that could not have been anticipated by the work of the 1960s.

For those who enjoy short story fiction, a much more lyrical version has been written by the award-winning novelist Alison MacLeod (MacLeod, 2011) in a collection of short stories, *Litmus*, published by Comma Press (Page, 2011*b*). Her story has been acclaimed by *The Sunday Times*, which published it in its Magazine section, and by the *BBC*, which short-listed it for its 2011 National Short Story Award. Is it true? My reply to her story (Noble, 2011*a*) begins with the question "Can fiction be truer than truth?" It may be a cliché but it is still a good question. She is more accurate than perhaps even she could know, but not in the ways that our science could tell her. Her accuracy lies in placing some of the science of the heart in the context of a much larger canvas of the heart in our culture, including the culture of love.

In fact, the science tells a rather more nuanced story from its own perspective. As the editor of *Litmus* says, "any historian of science will tell you that eureka moments don't actually exist". Stories are an "invaluable device for telescoping into the biography quickly, and grabbing some idealized, bite-sized science" (Page, 2011*a*). Alison MacLeod presents my eureka moment as being the discovery that $i_{K1}$ channels close on depolarization in the heart. That is true enough in the sense that I did feel sufficiently excited about it to interrupt Otto in a practical class to tell him the results that were emerging. But that alone was not a eureka moment in the sense that it was a completely new discovery. As I noted above, we had already found such channels in skeletal muscle.

That moment was rather a gradual realization through the mathematical modelling that many features of the cardiac action potential could be reproduced and understood when the properties of the cardiac potassium channels were incorporated into Hodgkin–Huxley-type equations. That discovery was deeply satisfying and it has been my good fortune to have been able to pursue the story through half a century of many further and surprising developments towards the project that is now called the cardiac physiome (Bassingthwaighte *et al.* 2009).

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# Substrates and triggers for the initiation of arrhythmias

The mechanisms by which the spread of electrical waves through the heart often becomes disturbed in patients with electrical and/or structural heart diseases, leading to cardiac rhythm disturbances, remain incompletely understood. We exposed a novel mechanism for arrhythmia initiation, in which areas of abrupt cardiac tissue expansion and alterations in the inward sodium current responsible for cardiac excitation set the stage for spontaneous premature local re-excitation and arrhythmogenesis.

## Cardiac fibrillation

Cardiac electrical and structural heterogeneities set the stage for the initiation of complex cardiac arrhythmias, including atrial fibrillation (AF), which is the major cause of embolic stroke, and ventricular tachycardia/fibrillation (VT/VF), which is the largest immediate cause of sudden cardiac death (SCD). However, little is known about how alterations in the morphological structure and the electrical organization of the myocardium act in concert to result in the initiation of either AF or VT/VF. Causal abnormalities may include: altered expression of proteins that form and/or modulate membrane ion channel function; remodelling of intercellular electrical and mechanical junctions; and pathological changes in the extracellular matrix with the development of fibrosis.

Patients with acquired heart diseases such as ischaemic heart disease and heart failure are the most susceptible to arrhythmias due to impairment of the normal spread of electrical waves. In these patients, altered ion channel function and structural remodelling leading to fibrosis result in substantial electrical and structural heterogeneity. However, it is unknown which combination of factors contribute to the sudden appearance of AF or VT/VF. Patients who suffer from inherited cardiac diseases such as channelopathies and hypertrophic cardiomyopathy also are highly susceptible to arrhythmias and have an increased risk of embolic stroke and SCD. A case in point is long QT syndrome (LQTS), an inheritable channelopathy with an electrocardiographic phenotype of QT-interval prolongation (corrected QT-interval, QTc > 440 ms). These patients present with syncope, arrhythmogenesis (particularly torsades de pointes) and SCD, with

David Auerbach (left) and José Jalife

the greatest prevalence during rest. Acquired LQTS can be manifested pharmacologically, or by electrolyte disturbances (hypokalaemia and hypomagnesaemia), structural heart disease or bradycardia. Many such patients are free of arrhythmias until one day the necessary conditions arise that lead to the onset of either AF or VT/VF. A great deal of research has been invested in understanding the conditions that initiate and maintain such arrhythmias, in an effort to develop novel strategies to prevent them.

Our recent study published in *The Journal of Physiology* (Auerbach *et al.* 2011) focused upon elucidating the substrate(s) and trigger(s) for the initiation of lethal arrhythmias. Specifically, in the presence of heterogeneous cardiac tissue architecture, we investigated the implications that alterations in the balance between depolarizing and repolarizing membrane ionic currents have upon the initiation of arrhythmias.

Previous work on arrhythmogenesis focused on anatomical or functional re-entry. However, little attention has been given to the possible role of the phenomenon of 'reflection' as a mechanism for the initiation and maintenance of arrhythmias. Reflection occurs when an electrical impulse that propagates along a narrow pathway returns spontaneously and prematurely along the same pathway, leading to extra beats and arrhythmia initiation. Reflection may occur if the pathway contains an area of impaired conduction (Antzelevitch *et al.* 1980) or a gradient in ion channel expression (Maoz *et al.* 2009). In our study, we demonstrated that reflection may depend on a structural heterogeneity consisting of a region of tissue expansion. A thin region of viable tissue that connected two wide regions of tissue promoted a transient local imbalance between inward and outward currents, prolongation of the action potential (AP) plateau, triggered activity (early after-depolarization, EAD), premature excitations and arrhythmogenesis. Most importantly, the possibility of reflection was significantly enhanced when structural defects combined with increased late or persistent sodium current ($I_{Na}$), such as seen in inherited and acquired cardiac electrical diseases.

## Heterogeneous cardiac tissue architecture

The heart is a very heterogeneous structure. Its muscle has varying wall thickness, anisotropic fibre orientation, microvasculature and trabeculation (Fig. 1*A*), all of which impact the dynamics of impulse propagation. These heterogeneities exist in structurally normal cardiac tissue, including the sinoatrial node, the atrioventricular node and the Purkinje–ventricular muscle junction (Fig. 1*B*). Also, heterogeneities are further exacerbated by pathological conditions, such as accessory pathways (e.g. Wolf–Parkinson–White Syndrome), ischaemia, infarction and fibrosis (e.g. arrhythmogenic right ventricular cardiomyopathy/dysplasia). As shown in Fig. 1*C*, narrow pathways of myocytes, surrounded by fibrotic or necrotic tissue, or inflammatory cells, often branch and merge, leading to tortuous, fragmented and unstable electrical impulse propagation.

Our recent study provides a novel mechanism for the initiation of arrhythmias, whereby abrupt geometrical expansions provide a substrate for re-excitation and reflection (Fig. 1*D–F*).

## Balance between depolarizing and repolarizing currents

The functional expression and biophysical properties of ion channels give the AP its characteristic shape. The $I_{Na}$ and L-type calcium current ($I_{CaL}$) are the two major depolarizing forces, while several potassium channel currents ($I_{to}$, $I_{Kr}$, $I_{Ks}$, $I_{K1}$) serve to repolarize the cell. The balance between depolarizing and repolarizing currents determines the level of excitability, AP morphology, and the dynamics of normal and re-entrant impulse propagation. When there is a reduction or altered kinetics in the depolarizing $I_{Na}$, there is a concomitant increase in the susceptibility for conduction slowing, block and arrhythmogenesis, particularly at regions of geometrical expansion.

Therefore, strategies to increase $I_{Na}$ density might serve as a potential anti-arrhythmic strategy. Recently Lau *et al.* (2009) used adenoviral transfer to express the skeletal muscle isoform of the sodium channel in the epicardial infarct border zone of the ventricle. In this zone there was an increase in the AP upstroke velocity, preserved fast conduction and a reduction in the incidence of inducible sustained VT/VF.

However, it is important to note that, when the depolarizing currents flowing during the AP plateau outcompete the repolarizing currents, for example, in LQTS type 3, a number of inherited mutations in the alpha subunit of the sodium channel result in the inability of $I_{Na}$ to completely

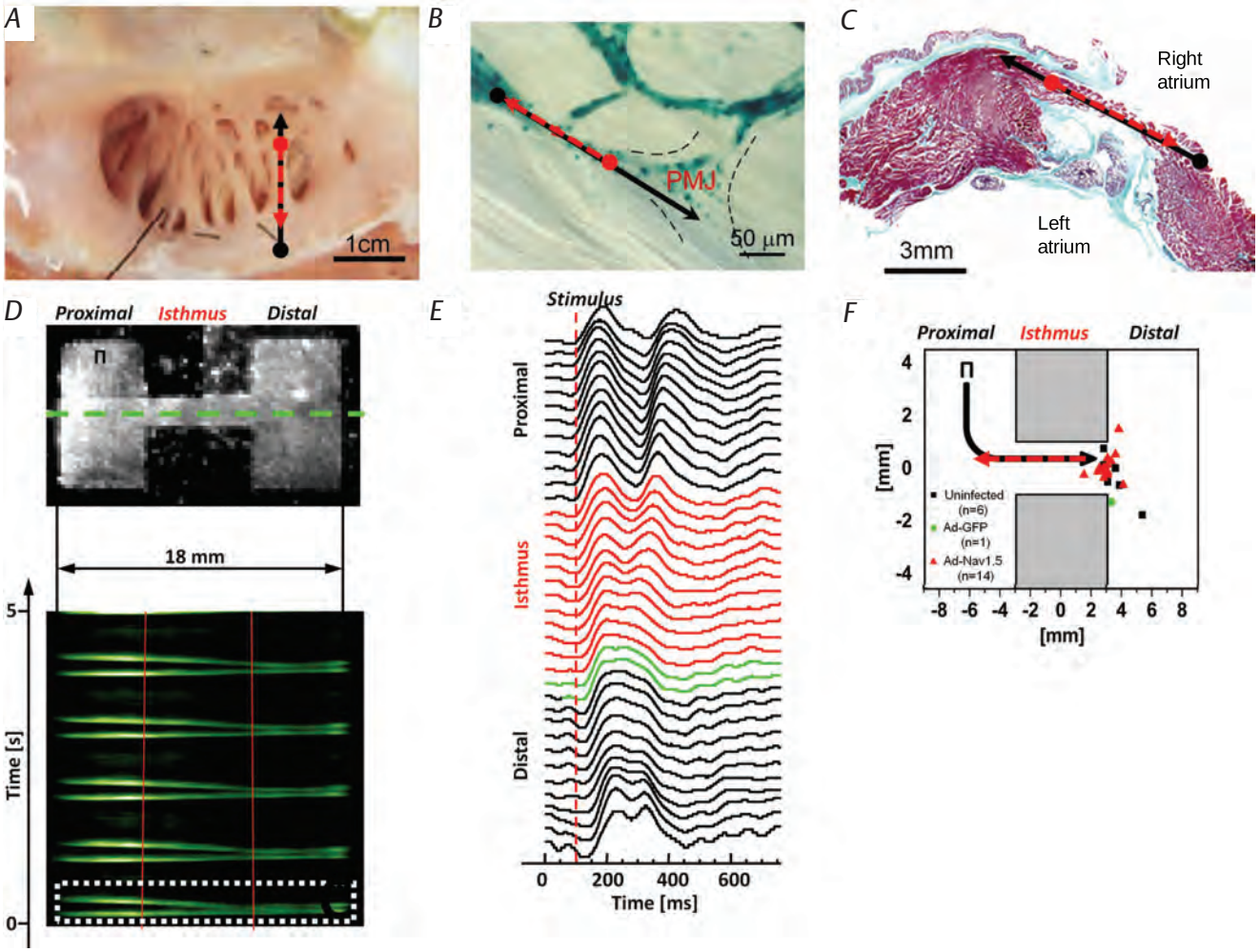


**Figure 1.** Heterogeneous cardiac structure. *A*, thin trabeculations connecting large regions of sheep right atrial tissue. *B*, Purkinje–ventricular muscle junction (PMJ) of the adult mouse visualized by LacZ staining of the Purkinje fibres. *C*, fibrotic tissue (light blue) deposits within the sheep atrial septum. In panels *A–C* note the thin bands of cardiac tissue that lead into abrupt geometrical expansions. *D*, top: patterned monolayer (2 mm wide isthmus) paced at 1 Hz (Π, site of stimulation). Bottom: average time–space plot for pixels along horizontal lines that traversed the isthmus (green dotted line in the top panel denotes one example.) The impulse originated on the upper proximal (left) side and activated the entire preparation distally (right, red vertical lines demark the structural heterogeneity), followed by re-excitation and reflection for each wave. *E*, optical APs across the preparation for wave 1 (white box in *D*). Red APs are from pixels within the isthmus and green APs are pixels within the first 500 µm of the distal expansion. *F*, diagram of the monolayer pattern with the site of re-excitation plotted. In panels *A–C* and *F*, black arrows in each panel depict the 1st electrical wave entering and travelling through the thin strand of cardiac tissue, and then exiting into the geometrical expansion. Red arrows illustrate the site of re-excitation at the distal expansion region with retrograde propagation, reflection. Panels *A–C* were graciously provided by Drs Omer Berenfeld, Karen L. Vikstrom and Matthew L. Klos.

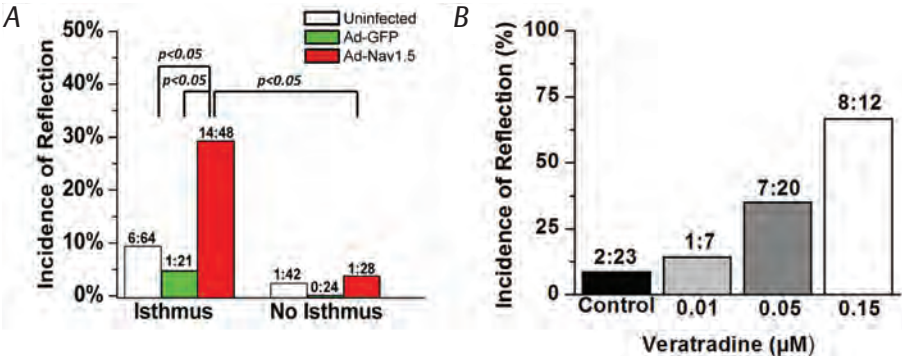


**Figure 2.** Structural and persistent $I_{Na}$ determinants of reflection. *A*, total incidence of reflection between each group and in the presence *vs*. absence of an isthmus. Chi square and Fisher Exact test. *B*, incidence of reflection at each concentration of veratridine (late/persistent $I_{Na}$ agonist, $P = 0.003$, Chi square test).

shut off during the AP. This results in the persistence of an inward current that contributes to prolongation of the AP plateau, with an increased susceptibility for triggered activity (EADs), premature excitation and arrhythmogenesis. Due to the great contributions of molecular biology, we have gained insights into the pathological remodelling in acquired cardiac disease (e.g. heart failure), as well as identified multiple inherited ion channel mutations. Patients with acquired and inherited ion channel diseases are vulnerable to SCD. For instance, genetic screening has implicated channelopathies as a cause of sudden infant death syndrome and sudden unexplained death in epilepsy.

## Advancing the understanding of arrhythmogenesis

In our study, adenovirally- and pharmacologically-increased persistent $I_{Na}$ led to prolongation of the AP duration, EADs and reflection (Fig. 2), thus serving to model LQTS type 3.

A substrate (structural heterogeneity) and a trigger (increased persistent $I_{Na}$) combined to promote life-threatening arrhythmia initiation. As illustrated in Fig. 3, the abrupt geometrical expansion provided ideal conditions for retrograde electrotonic flow of depolarizing current into a region of high input resistance (i.e. thin strand of tissue) at a time of high membrane resistance (i.e. AP plateau).

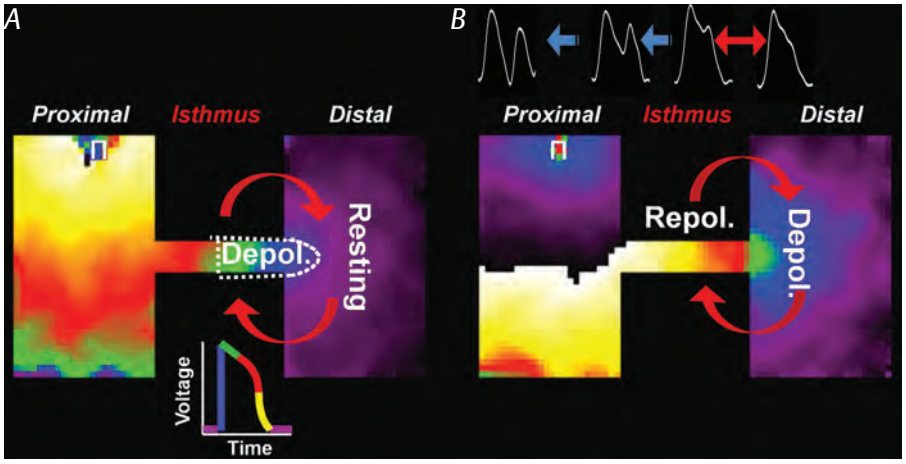


**Figure 3.** Schematic representation depicting our explanation for the mechanism of re-excitation and reflection at the isthmus. *A*, as the depolarizing wavefront (blue) entered the distal expansion there was a strong voltage gradient and repolarizing electrotonic current flowed from the expansion into the isthmus, which led to conduction slowing and block (Π, site of pacing). *B*, upon depolarization of the distal region, the voltage gradient was reversed as there was a large area at the depolarized state, while the small area within the isthmus was beginning to repolarize. This resulted in AP duration prolongation at the expansion. Depolarizing electrotonic current flowed into the cells within the isthmus, which faced a high input impedance and membrane resistance. Consequently, there was re-excitation at the distal expansion, which led to reflection.

Our study provides a potential explanation for why patients with LQTS may be free of arrhythmias for many years until external factors (e.g. changes in the autonomic input to the heart, electrolyte imbalance, increased fibrosis, etc.) force the relation between substrate and trigger to reach a critical level at which time reflection, EADs and premature excitation occur. In patients with LQTS, coronary artery disease is an independent and significant risk factor increasing the incidence of LQTS-related cardiac events (Sze *et al.* 2008).

In conclusion, our model provides a new framework to examine the role that cardiac structure and alterations in ion channel expression and function have upon arrhythmogenesis. Results from our study offer insights into which patients may be at the greatest risk of arrhythmias initiated by reflection, and may subsequently provide clues towards targeted therapies to prevent the onset of VF.

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# Axonal filtering as a mechanism of deep brain stimulation in Parkinson's disease

Deep brain stimulation (DBS) in Parkinson's disease is a telling example of how the understanding of the basic principles governing basal ganglia function in the normal and diseased brain provided the rationale for a precisely targeted electro-invasive therapy. Nevertheless, the exact beneficial mechanisms of DBS at the cellular, synaptic and systemic level remain elusive. Our research emphasizes attenuation of axonal excitability as an important mechanism of DBS to abrogate pathological firing patterns.



Left to right: Fang Zheng, Jens Volkmann and Christian Alzheimer

Neurophysiological recordings from basal ganglia in Parkinson's disease (PD) and in animal models thereof showed that the progressive loss of dopaminergic neurons in the substantia nigra pars compacta, which represents the neuropathological hallmark of PD, leads to abnormally synchronized burst firing and oscillations (Rivlin-Etzion *et al.* 2006). Most importantly, neurons of the subthalamic nucleus (STN), which are the only glutamatergic neurons of the basal ganglia, appeared to be located in a prime position to drive and maintain these pathological firing patterns. Consequently, surgical ablation of STN produced strong relief from the cardinal motor symptoms of PD, comprising akinesia, rigidity and tremor. Lending strong support to the notion that inactivation of STN neurons is essential to improve motor deficits in PD, stereotactic microinjection of the local anaesthetic lidocaine into the STN reversed the motor symptoms of PD patients (Levy *et al.* 2001).

In contrast to the irreversible tissue damage of surgical lesion and the transient effect of drug microinjection, electrical stimulation of STN neurons by implanted microelectrodes affords a reversible, but lasting method to modify aberrant discharge activity in the basal ganglia circuitry of PD patients. Although introduced in the 1990s and now widely employed as an effective electro-invasive therapy, it is still debated how DBS achieves its therapeutic benefits (Hammond *et al.* 2008; Deniau *et al.* 2010; Krack *et al.* 2010). Notably, DBS is only effective if administered at high frequency (~130 Hz), and the improvement of motor deficits displays a rapid onset and decline with the make and break of STN stimulation, respectively.

Since STN-DBS strongly mimicked the therapeutic effects of either neurosurgical ablation or lidocaine injection in PD patients, it seemed at first plausible to assume that the high-frequency electrical stimulation produces an almost immediate and quickly reversible inhibition of STN neurons, most probably involving a depolarization block of intrinsic excitability (Beurrier *et al.* 2001). However, the original notion that DBS stymies all neuronal activity within the STN was challenged by recordings from PD patients, in whom DBS failed to silence STN neurons (Carlson *et al.* 2010). Further contradiction was gathered at the other end of the experimental scale, where patch-clamp recordings from rodent STN neurons showed that these cells were well capable of following high-frequency stimulation with single action potential firing. What was strongly compromised, however, was the ionic mechanism generating burst discharges. Thus, it was argued that DBS reinstates physiological firing by 'jamming' pathological burst discharges (Do & Bean, 2003).

Whereas these studies were devoted to the local effects of DBS within the STN, it remained to be determined to what extent the high-frequency electrical stimuli delivered to the STN are transmitted to other regions within and even outside the basal ganglia. Remember, for example, that the STN is not only part of the 'indirect' pathway of the basal ganglia, but also receives a 'hyperdirect' corticosubthalamic input that might be activated antidromically by DBS. Within the basal ganglia network, STN-DBS might activate target neurons in the substantia nigra pars compacta, thereby possibly driving dopaminergic neurons, as well as target neurons in the output structures (internal globus pallidus and substantia nigra pars reticulata), thereby modifying central motor controls. Although experimental evidence for such network effects has been advanced (Deniau *et al.* 2010), concerns remain as to whether axons will faithfully conduct the high frequency of DBS over time.

To explore this issue in a preparation that allowed us to directly examine axonal excitability, we used a rat brain slice preparation preserving the STN and its projections to the substantia nigra and the entopeduncular nucleus, which is the rodent equivalent of the internal globus pallidus (Zheng *et al.* 2011). By placing the stimulating electrode in the STN and one

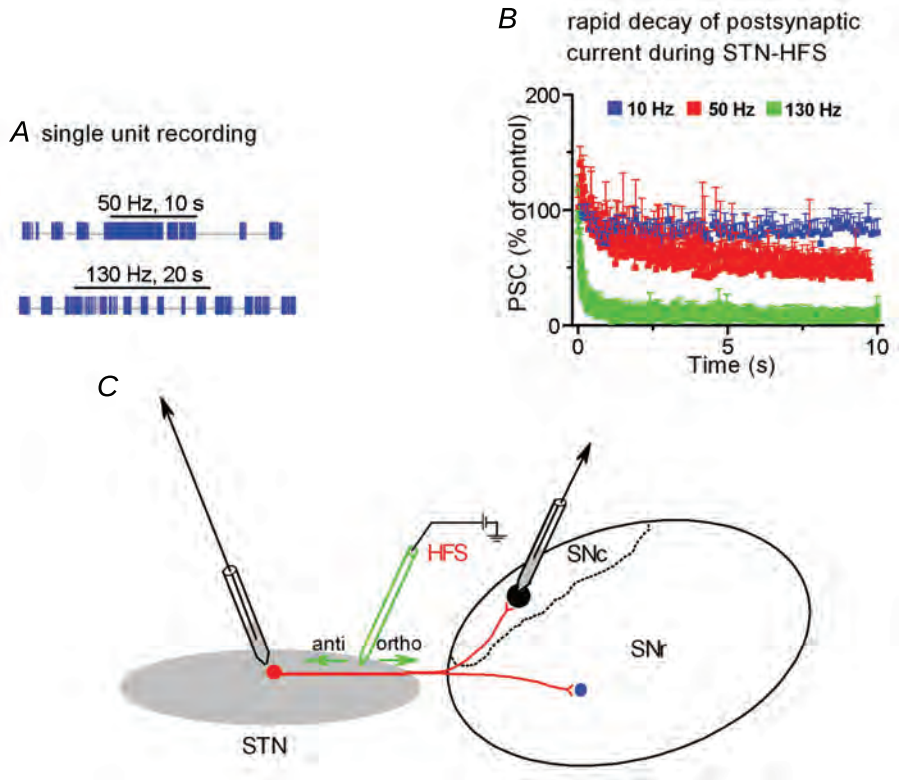


**Figure 1.** *A*, effects of high-frequency stimulation (HFS) within the subthalamic nucleus (STN) on single unit activity recorded by an extracellular electrode from an antidromically activated STN neuron exhibiting a spontaneous burst firing pattern. Whereas the therapeutically ineffective stimulation at 50 Hz produces a massive increase in firing (upper trace), high-frequency stimulation at 130 Hz only transiently enhanced firing before the intrinsic bursting resumed, albeit with shorter burst durations and longer burst intervals. *B*, effects of HFS in the STN on postsynaptic potentials recorded in the whole-cell patch-clamp configuration from an orthodromically activated neuron in the substantia nigra pars compacta (SNc). The plot summarizes the changes in normalized PSC amplitudes during stimulus trains, demonstrating the time- and frequency-dependent effects of STN stimulation (10 Hz, $n$ = 10; 50 Hz, $n$ = 10; 130 Hz, $n$ = 9). Averaged PSC amplitudes at the end of train were 82 ± 11%, 48 ± 11% and 12 ± 8% of control for 10 Hz, 50 Hz and 130 Hz, respectively. *C*, schematic drawing illustrating the recording configurations in *A* and *B*. SNr, substantia nigra pars reticulata. (*A* and *B* were adapted from Zheng *et al.* 2011.)

recording electrode also in the STN or in one of its target regions, we were able to monitor firing activity of antidromically activated STN neurons as well as axonal conduction and synaptic transmission in orthodromically activated target regions before, during and after high-frequency stimulation (Figs 1*C* and 2*C*).

When recording single unit activity from an antidromically activated STN neuron, high-frequency stimulation did not abrogate its spontaneous firing, but modified its burst firing pattern towards shorter burst durations and longer inter-burst intervals (Fig. 1*A*, lower trace). This observation is consistent with the above notion that DBS does not silence STN neurons, but impairs their propensity to generate bursts.

In orthodromically connected neurons of the substantia nigra pars compacta, whole-cell patch-clamp recordings demonstrated a rapid decline of postsynaptic currents during high-frequency stimulation in the STN (Fig. 1*B*). Did this striking run-down result from the exhaustion of synaptic mechanisms or rather from conduction failure in afferent fibres? We resolved this issue by directly recording isolated fibre volleys, which are field potentials generated by axonal action potentials (Fig. 2). As shown in Fig. 2*A* and *B*, fibre volleys arising in different projections all rapidly declined during high-frequency STN stimulation. These data identified axonal failure as an important mechanism of DBS. Axonal failure uncouples the STN from upstream and downstream regions, thereby shielding the network against aberrant firing.

Why does DBS overburden the capacity of axons to transmit signals at high frequency? Model calculations (Bellinger *et al.* 2008) and our own experimental data favour a scenario in which accumulation of $K^+$ in the submyelin space surrounding the axon and the concomitant depolarization render axonal $Na^+$ channels inactivated. As axonal firing is progressively abating, however, $K^+$ levels should fall again and $Na^+$ channels should partially recover, explaining the intermittent synaptic responses that we observed during maintained high-frequency stimulation in STN target regions. Thus, DBS does not simply shut down incoming and outgoing

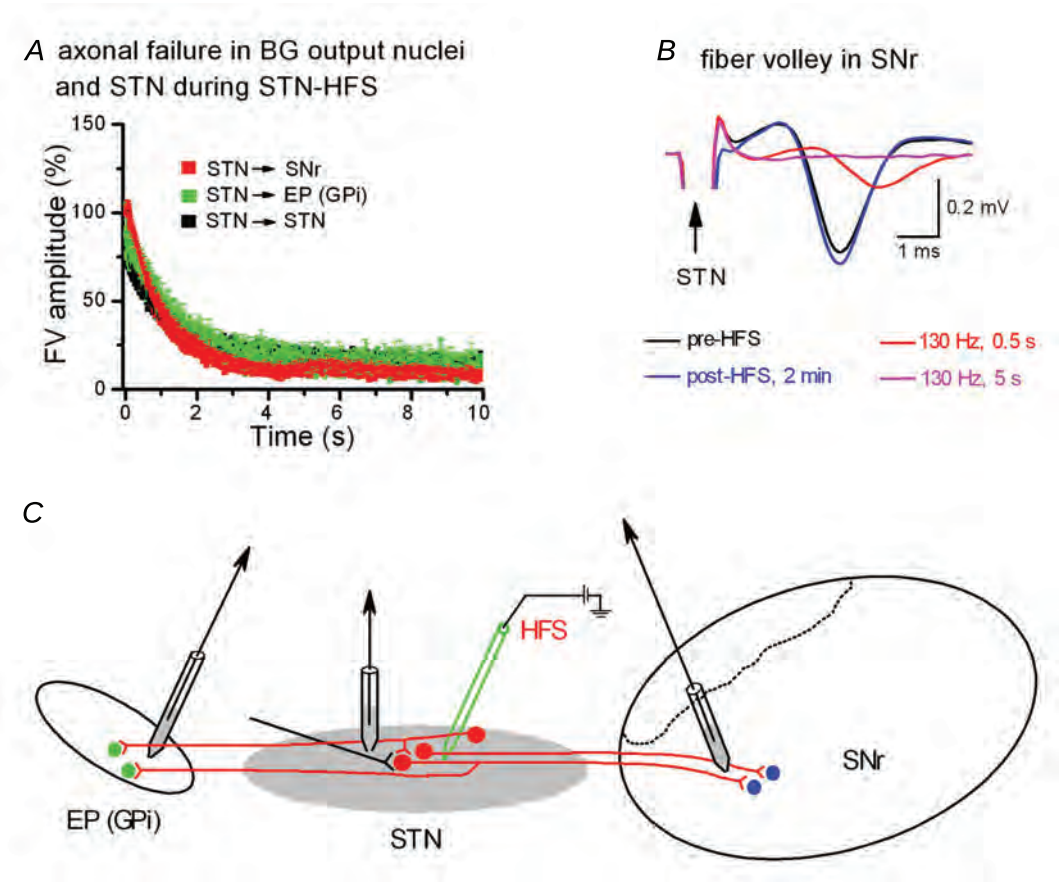


**Figure 2.** *A*, plot of normalized fibre volley (FV) amplitudes during STN-HFS recorded within STN ($n$ = 9), in substantia nigra pars reticulata (SNr, $n$ = 7) and in entopeduncular nucleus (EP, $n$ = 6). FVs were recorded by extracellular electrodes placed into different basal ganglia (BG) regions as schematically illustrated in *C*. FVs were functionally isolated from synaptic potentials by pharmacological suppression of glutamatergic and GABAergic synapses and by reduction of extracellular $Ca^{2+}$. Averaged FV amplitudes at the end of HFS were 15 ± 2%, 8 ± 2% and 12 ± 2% of control for STN, SNr and EP, respectively. *B*, superimposed FVs recorded in SNr in response to STN stimulation (arrow, 90 µs, 200 µA) at different time points before, during and after HFS as indicated. *C*, schematic drawing illustrating the recording configurations in *A* and *B*. (*A* and *B* were adapted from Zheng *et al.* 2011.) GPi, internal globus pallidus.

projections to and from the STN as well as fibres of passage, but rather imposes a filter that eliminates pathological firing. By emphasizing axonal filtering as the prevailing mechanism of DBS, our research should reconcile the apparent discrepancy between the original concept that DBS locally inhibits the STN akin to surgical lesion with more recent data demonstrating remote effects in the basal ganglia network.

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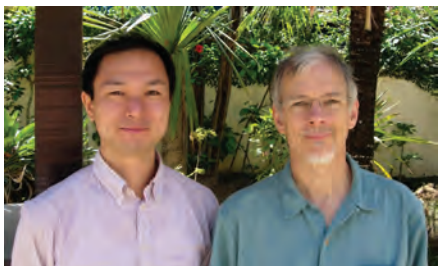
# Central neural circuitry for shivering

Shivering is a fundamental physiological response that occurs in skeletal muscles to produce heat when it is cold or during the development of fever. This response is initiated and maintained by the central nervous system. Recently, we elucidated the central circuitry mechanism that drives shivering. Interestingly, the neural pathway for shivering overlaps anatomically with that for metabolic thermogenesis in brown adipose tissue.

Appropriate regulation of body temperature is essential to our life. To survive in cold environments, mammals, including humans, must compensate for lost body heat by activating heat production (thermogenesis) mechanisms within the body. Also to combat infection, heat production is increased to develop fever. Such cold-defense and febrile responses involve two modes of thermogenesis: shivering thermogenesis and non-shivering (metabolic) thermogenesis. Shivering thermogenesis is driven by the somatomotor system and occurs in skeletal muscles. Non-shivering thermogenesis is driven by the sympathetic nervous system and occurs primarily in brown adipose tissue. The somatic and sympathetic motor systems mediating these thermogenic responses are governed by the central nervous system.

The thermoregulatory centre in the brain is located in the preoptic area, the most rostral structure in the hypothalamus. The preoptic area receives information on environmental temperature from cutaneous cool and warm receptors (Nakamura & Morrison, 2008*a*, 2010) and provides command signals to peripheral effectors to drive thermoregulatory responses (Nagashima *et al.* 2000; Romanovsky, 2007; Morrison *et al.* 2008). We have previously reported the descending neural pathway from the preoptic area that drives non-shivering thermogenesis in brown adipose tissue (Nakamura & Morrison, 2007, 2008*b*). In contrast, the mechanism through which central commands for shivering are transmitted from the preoptic area to skeletal muscle has been uncertain, despite the fact that shivering is a well-noticed cold-defensive response.



Kazuhiro Nakamura (left) and Shaun Morrison

In our recent study reported in *The Journal of Physiology*, we simultaneously recorded electromyogram to measure shivering as well as brown adipose tissue temperature to measure non-shivering thermogenesis in anaesthetized rats (Nakamura & Morrison, 2011). This experiment was to examine whether the brain sites that mediate non-shivering thermogenesis are also involved in shivering. At first, this possibility seemed unlikely, because these two thermogenic responses are mediated by the different motor systems that, under normal circumstances, are controlled independently. However, unexpectedly, nanoinjections of drugs into the brain regions that have been known to mediate brown adipose tissue thermogenesis (Nakamura & Morrison, 2007) exerted parallel effects on both thermogenic responses (Nakamura & Morrison, 2011).

Briefly cooling the trunk skin of the rats consistently evoked both shivering in nuchal (neck) muscles and non-shivering thermogenesis in brown adipose tissue (Nakamura & Morrison, 2011). Inhibition of neurons with nanoinjections of muscimol into the median preoptic nucleus, which is a preoptic subregion that receives thermosensory signals from skin thermoreceptors (Nakamura & Morrison, 2008*a*, 2010), eliminated both shivering and non-shivering thermogenesis evoked by skin cooling (Fig. 1*A*) (Nakamura & Morrison, 2011). Furthermore, stimulation of neurons in the same preoptic subregion elicited shivering and non-shivering thermogenesis, mimicking skin cooling (Nakamura & Morrison, 2011). These results indicate that an input of cutaneous cool-sensory signals into the preoptic area is a required cue to elicit shivering and non-shivering thermogenesis for cold defense.

Mimicking fever by application of prostaglandin (PG) $E_2$, a pyrogenic mediator, into the preoptic area also elicits both shivering and non-shivering thermogenesis. Both thermogenic responses evoked either by skin cooling or $PGE_2$ injection were eliminated by inhibition of neurons in the dorsomedial hypothalamus or in the rostral medullary raphe pallidus nucleus (Fig. 1*B* and *C*) (Nakamura & Morrison, 2011). Therefore, we concluded that neurons in these brain regions integrate descending command signals from the preoptic area leading to shivering and non-shivering thermogenesis. However, because skin temperature thresholds to elicit these thermogenic responses during cooling were different, separate populations of neurons in these brain regions appear to mediate these responses.

Activation of 5-$HT_{1A}$ receptors in the rostral raphe pallidus nucleus with local nanoinjection of an agonist also eliminated the shivering and non-shivering thermogenesis evoked by skin cooling or $PGE_2$ injection (Nakamura & Morrison, 2011). Although the source of the serotonin that might normally activate these 5-$HT_{1A}$ receptors is unknown, it is

clear that ligands binding to 5-$HT_{1A}$ receptors, potentially located on somatic and sympathetic premotor neurons (Helke *et al.* 1997), in this rostral medullary raphe region, can exert a potent inhibitory effect on cold-defensive thermogenic responses, which probably contributes to the hypothermic effects of anti-depressant drugs that bind to 5-$HT_{1A}$ receptors.

Based on these and earlier findings, we propose a model of the neural pathways for the regulation of shivering and non-shivering thermogenesis. Under warm environments (Fig. 2, left), warm-sensory signals from the skin ascend to the preoptic area and activate inhibitory projection neurons in the medial preoptic area, which tonically inhibit thermogenic signalling outflows. Under cool (or cold) environments (Fig. 2, right), cutaneous cool-sensory signals activate local inhibitory neurons in the median preoptic nucleus, which then reduce the activity of the inhibitory projection neurons in the medial preoptic area. In the case of infection, $PGE_2$, which is produced in response to inflammatory cytokine signals, also inhibits the projection neurons in the medial preoptic area through the EP3 receptor. The cooling- or $PGE_2$-mediated inhibition of these projection neurons leads to disinhibition of neurons in the dorsomedial hypothalamus, which, in turn, activate somatic and sympathetic premotor neurons

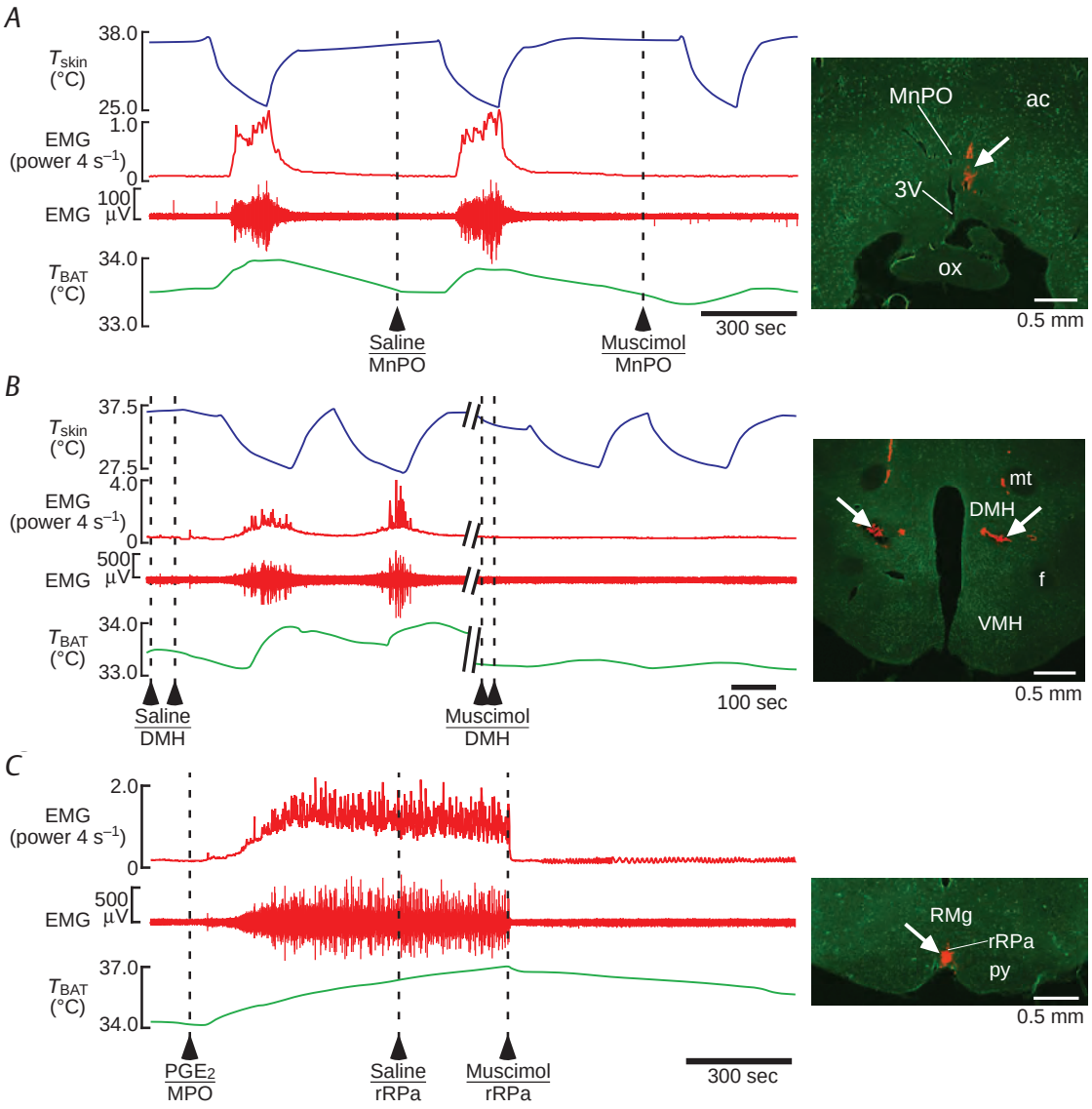



**Figure 1.** Shivering in skeletal muscles and non-shivering thermogenesis in brown adipose tissue (BAT) are eliminated by neuronal inhibition in hypothalamic and medullary thermoregulatory sites in anaesthetized rats. Increases in electromyographic activity (EMG) in nuchal muscles and in the temperature of interscapular BAT ($T_{BAT}$) that were evoked by cooling the trunk skin ($T_{skin}$) (*A* and *B*) or by a nanoinjection of $PGE_2$ into the medial preoptic area (MPO) (*C*) were eliminated by nanoinjection of muscimol, a $GABA_A$ receptor agonist acting as a neuronal inhibitor, into the median preoptic nucleus (MnPO) (*A*), the dorsomedial hypothalamus (DMH) (*B*) or the rostral raphe pallidus nucleus (rRPa) (*C*). Micrographs show representative views of injection sites in each hypothalamic or medullary region (clusters of fluorescent microbeads indicated by arrows). 3V, third ventricle; ac, anterior commissure; f, fornix; mt, mammillothalamic tract; ox, optic chiasm; py, pyramidal tract; RMg, raphe magnus nucleus. From Nakamura & Morrison (2011).

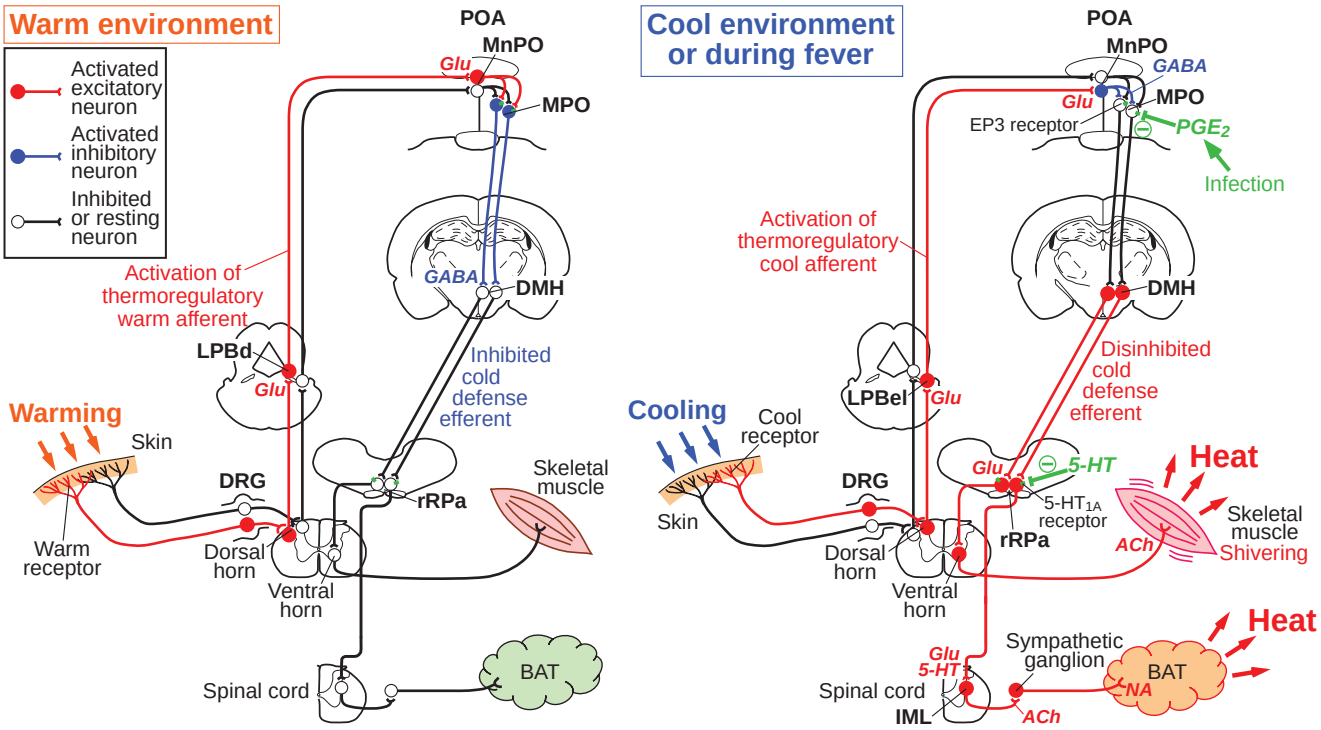
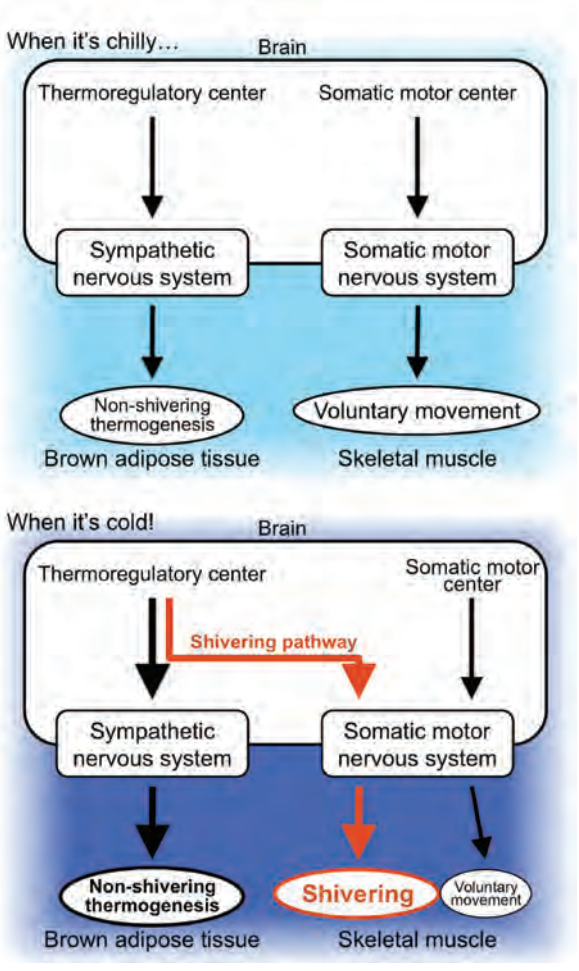



**Figure 2.** Model of the neural pathways for shivering and non-shivering BAT thermogenesis. For detail, see the text. ACh, acetylcholine; DRG, dorsal root ganglion; Glu, glutamate; IML, intermediolateral cell column; LPBd, dorsal part of the lateral parabrachial nucleus; LPBel, external lateral part of the lateral parabrachial nucleus; NA, noradrenaline; POA, preoptic area.




in the rostral medullary raphe. The activated premotor neurons finally excite spinal somatic and sympathetic motor outputs, driving shivering and non-shivering thermogenesis, respectively.

Our findings establish the interesting concept of parallel central outflow pathways from the thermoregulatory centre that drive thermogenesis mediated by the sympathetic nervous system and the somatic motor system. Normally, the somatic motor system is responsible for establishing and coordinating voluntary movements and is controlled by central mechanisms independent of those controlling the

**Figure 3.** Scheme of the central regulation of the sympathetic nervous system for BAT thermogenesis and the somatic motor nervous system for voluntary movements and shivering. These two nervous systems are independently controlled normally (top). However, when high heat production is demanded (bottom), the shivering efferent pathway (red) from the thermoregulatory centre is activated and drives the somatic motor system to evoke shivering. As a result, voluntary movements are hampered.

sympathetic nervous system (Fig. 3, top). However, when an enhanced level of heat production is required to maintain thermal homeostasis or to develop fever (Fig. 3, bottom), involuntary commands from the thermoregulatory centre drives the somatic motor system to produce the stereotyped motor pattern of shivering. When this involuntary signalling is intense, it becomes difficult to produce fine motor tasks, such as speaking and writing, a common experience in cold winter weather.

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# Is –110°C cold air cryotherapy effective in improving post-exercise recovery in sports people?

Whole body cryotherapy (WBC) involves repeatedly exposing an individual, dressed in minimal clothing, to extremely cold air (–100 to –130°C) for a short period. One specific claim that is often made is that WBC is effective in treating exercise-induced muscle soreness and damage. However, our results suggest that two bouts of WBC were ineffective in improving recovery from eccentric exercise when administered 24 hours after eccentric exercise.

Whole body cryotherapy (WBC) is a cooling treatment that has recently gained widespread popularity amongst athletes, with a range of claims being made regarding its efficacy, particularly in aiding recovery from training. WBC involves repeatedly exposing an individual, dressed in minimal clothing, to extremely cold air (–100 to –130°C) for 2 to 4 minutes (Costello *et al.* 2011). During WBC, the individual experiences temperatures that are between 30–50°C colder than the lowest temperature ever recorded in Antarctica. Consequently, WBC is causing much debate amongst physiologists, physiotherapist, clinicians and sports people alike regarding its effectiveness and potential risks. This debate has intensified with the news that former 100 m Olympic Champion Justin Gatlin suffered frostbite after visiting one of these chambers (www.bbc.co.uk). The cause of this incident was most probably wet socks; the extreme cold can rapidly penetrate shoes through direct contact with the ground. Though the skin is exposed to the cold during WBC (many WBC participants just wear shorts), the relatively low thermal conductivity of air, lack of air movement and the short duration of exposure normally reduce the risk of cold injury. Most operators also ensure that the participants wear gloves and facemasks. WBC chambers were introduced from Japan to Europe in 1982 and the use of this treatment continues to rise despite the paucity of published literature in the area. International athletes, including rugby players, soccer players and track and field athletes, have reported using WBC as a method of recovery from sports training and competition. WBC is being promoted in sports medicine as a treatment for muscle injuries, syndromes of overuse and to enhance recovery between training sessions (Banfi *et al.* 2009). One specific claim that has been made is that WBC is effective in treating exercise-induced muscle soreness and damage. We have undertaken a study to evaluate WBC treatment effectiveness on indices of muscle function or soreness following an exercise bout specifically designed to induce a moderate level of temporary, repairable muscle damage.

Joseph Costello (left) and Alan Donnelly

The hypothesis of the current study was that WBC would be no more effective on muscle soreness recovery following eccentric exercise than a sham treatment (Costello *et al*. 2011). To address this hypothesis, we conducted a randomised controlled laboratory study in a two-group design (control and treatment). Despite the growing

use of WBC, this was the first study of its kind to assess the effects of WBC treatment on recovery from muscle-damaging exercise. A group of 18 healthy and active participants with a mean age of 21.2 ± 2.1 years, who were blinded to the hypothesis of the study, performed an eccentric exercise bout consisting of 100 high-force maximal eccentric contractions of the left knee extensors on an isokinetic dynamometer (a device that measures muscle strength). These 18 volunteers were randomly assigned to either a WBC group (7 males and 2 females) or a control group (7 males and 2 females). Twenty-four hours later the participants received two bouts of either WBC or the control treatment 2 hours apart. The WBC treatment consisted of the subjects standing in a pre-cooling room at –60 ± 3°C for 20 seconds before entering and walking slowly around a second room at –110 ± 3°C for 3 minutes. In the control group, the subjects followed the same procedure as the WBC except both chambers were set at a temperature of 15 ± 3°C. Maximal voluntary isometric contraction force (MVIC) of the left knee extensors and subjects' subjective assessment of muscle soreness was measured immediately before and after the exercise bout and at 48, 72 and 96 hours following eccentric exercise. MVIC (which was reduced by 40%) and the subjects' subjective assessment of muscle soreness were both significantly affected in both groups, compared to baseline, following the eccentric exercise. Although no biopsies were collected in this study, the force loss recorded is indicative of underlying muscle damage. These outcome measures did not return to baseline for at least 96 hours following the exercise bout, and there were no differences between the WBC and the control group at any time-point during recovery. The results of this study suggest that two bouts of WBC were ineffective in improving recovery from eccentric exercise when administered 24 hours after eccentric exercise. However, it should be noted that recent studies suggest that WBC might have an anti-inflammatory effect (Banfi *et al.* 2009; Pournot *et al.* 2011).

Further research studies we have undertaken addressed the possible effects cryotherapy may have on proprioceptive acuity. We have previously systematically reviewed (Costello & Donnelly, 2010) and studied (Costello & Donnelly, 2011; Costello *et al*. 2011) the effects of cold on proprioception, in the form of joint position sense, and concluded that until further evidence is provided, clinicians and coaches should be cautious when returning individuals to tasks requiring components of proprioceptive input immediately after a cryotherapy treatment (Costello & Donnelly, 2010). Proprioceptive or positional sense deficits following cryotherapy could be attributed to a reduction in tissue temperatures, nerve conduction velocity, the eventual blocking of conduction and alterations in motor output. However, to date there has been little research in this area and it may warrant further investigation. The potential of cold-induced reductions in proprioception following WBC is especially important for elite athletes who have reported using WBC before or between sessions on the same day. In a sample of 36 healthy volunteers we found that force proprioception, joint position sense and MVIC of the knee extensors were unaffected following WBC exposure and that WBC does not increase the risk of proprioceptive-related injury (Costello *et al.* 2011). Consequently, individuals who choose to utilise this protocol of WBC before a training session or athletic participation do not appear to be at a higher risk of proprioceptive-related injury.

In summary, WBC is rapidly gaining popularity amongst athletes and sports people. To date there has been no convincing, unequivocal support for the therapy's effectiveness in improving muscle functional recovery published in the peer-reviewed literature. Despite this, individuals continue to use WBC protocols that lack rigorous physiological assessment, and may perhaps be of limited value. Finally, WBC does not reduce proprioceptive acuity but chamber operators, clinicians and sports people need to be continuously vigilant of the potential of the technique to result in cold-induced injury.

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# Mice deficient in endothelin-3 gene lack pain perception from the terminal gastrointestinal tract

In many different types of mammal, endothelin peptides and their endogenous receptors have been shown to play a major role in nociception in a variety of visceral and somatic organs. Here, we report that mice with a genetic mutation in the endothelin-3 gene have a major sensory deficit in a specific class of low-threshold wide dynamic range spinal afferent nerve that innervates the colorectum. Functionally, these mice display a loss of mechano-nociception selectively from the colorectum, whilst pain perception from other internal and somatic organs remains unaffected.

Intense distension or contraction (spasm) of different regions of the gastrointestinal (GI) tract is well known to lead to the conscious sensation of pain in both laboratory animals and human beings. However, identifying exactly which specific classes of sensory fibres detect painful stimuli *in vivo* throughout the different regions of the GI tract has been difficult to elucidate. Pain arising from all internal (visceral) organs is detected and transmitted to the spinal cord via spinal afferent neurons, whose cell bodies lie in the dorsal root ganglia. Consequently, there has been substantial clinical interest in identifying exactly which classes of spinal afferent could be targeted to develop therapies that might selectively target and silence 'pain-sensing' neurons. Unfortunately, this has been a difficult question to address because it is clear that the spinal afferent innervation of the lower GI tract contains at least four to five different classes of sensory fibre, each of which responds to different types and intensities of stimulation (Brierley *et al.* 2004).

Substantial evidence has been presented that endogenous endothelins and their receptors participate in a wide range of nociceptive behaviours (Baamonde *et al*. 2004; Khodorova *et al*. 2009; Stösser *et al*. 2010). It is also well known that genetic mutations that lead to a loss of endothelin peptides, or their cognate receptors, lead to developmental defects in the gut wall such as loss of intrinsic neurons in the terminal gastrointestinal tract – a condition known as congenital aganglionosis, or Hirschsprung's disease in humans.

From top left clockwise: Nick Spencer, Simon Brookes and Vladimir Zagorodnyuk.

Our recent work has focused on the spinal afferent innervation of the colorectum in a mutant strain of mouse that is deficient in a gene known as endothelin-3 (ET-3). This gene encodes production of the endothelin peptide, whose function in sensory neurophysiology in the gastrointestinal tract has been difficult to establish. However, we recently made a major advance in our laboratory in identifying that mice lacking the ET-3 gene fail to detect pain following noxious colorectal distension (see Fig. 1 and Zagorodnyuk *et al*. 2011). Only at the highest distension pressures tested was any pain response elicited in ET-3-deficient mice (Fig.1). In contrast, robust visceromotor responses (VMRs) could be evoked in wild type mice with stimuli over 20 mmHg. An interesting observation we found in our study was that this sensory deficit was specific for the colorectum (Zagorodnyuk *et al*. 2011). In other words, loss of pain perception from the colorectum did not reflect a generalized deficit in central sensory or motor pathways, since responses to both bladder distension (a visceral stimulus) and tail and hind limb compression (somatic stimuli) were normal in ET-3-deficient mice (see Fig. 2 and Zagorodnyuk *et al*. 2011). Thus, the deficit lay specifically in the sensory pathways to the distal bowel of ET-3-deficient mice. We then tested whether the neural pathway that normally detects and encrypts pain perception was present and intact in colorectum of ls/ls mice. To test this, we applied fine electrical stimulating wires to the surface of the aganglionic colorectum (*in vivo*) and found we could still evoke visceromotor responses in ls/ls mice, albeit these responses were significantly smaller than those in wild type mice. This showed that the loss of pain perception was not due to the loss of a pain pathway or spinal circuitry required for pain reflexes *in vivo*.

In earlier studies we had shown that low-threshold, stretch-sensitive rectal afferents innervated the smooth muscle of the aganglionic colorectum in mice with mutations in either the gene encoding ET-3 or the endothelin-B receptor (Ednrb) (Spencer *et al.* 2008*a*,*b*). We were able to identify which specific classes of afferent might be impaired. We identified that loss of pain perception in ET-3-deficient mice was due to a specific reduction in the density and mechanosensitivity of a class of low-threshold, wide dynamic range stretch-sensitive rectal afferents (Fig. 2). This class of sensory fibre was known as either a muscular or muscular/mucosal afferent, which responded to stretch and/or mucosal stimulation.

Four classes of pelvic/sacral afferents have been identified in the mouse

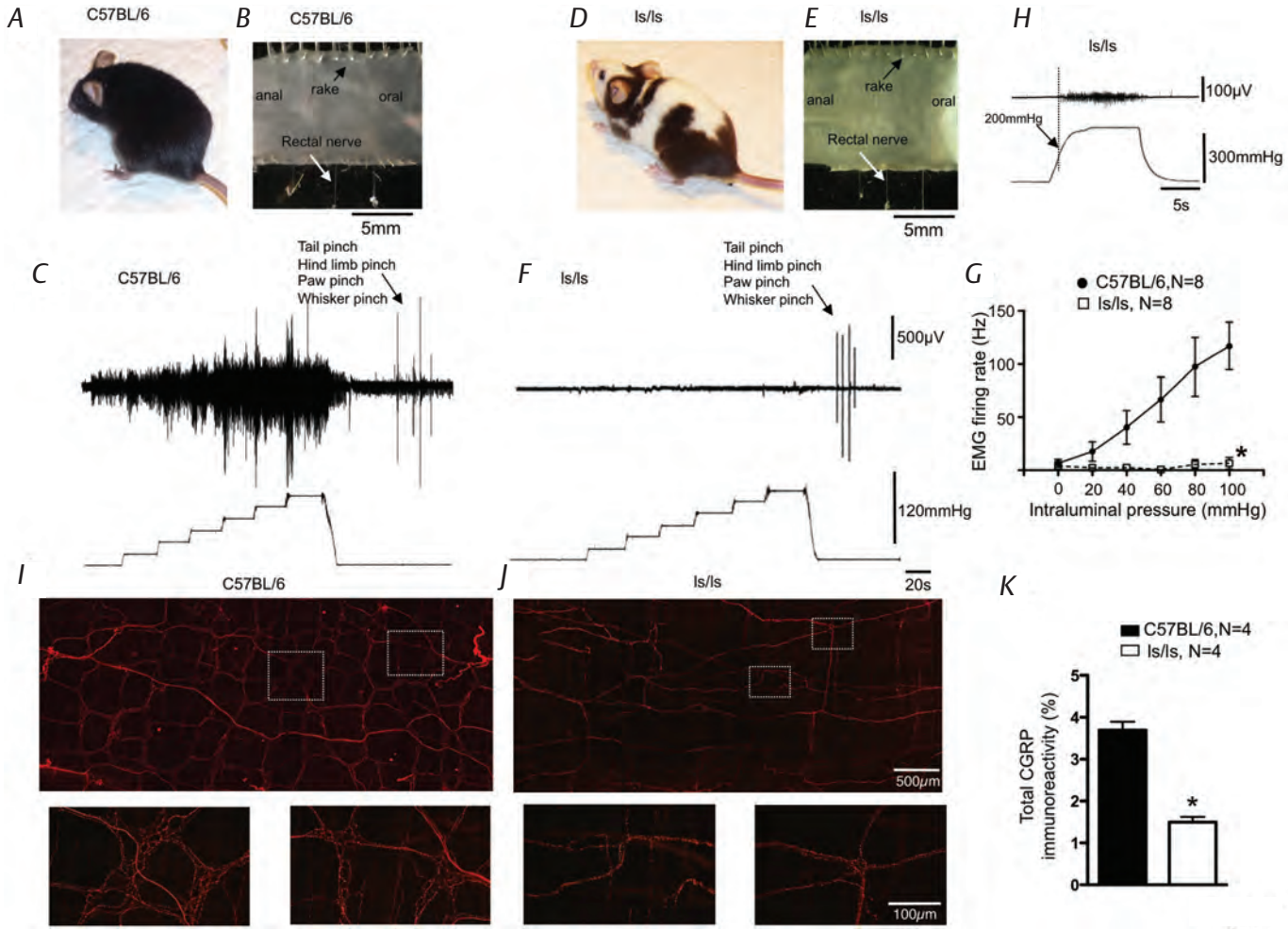


**Figure 1**. Loss of visceromotor responses to rectal distension in ls/ls mice. *A*, control C57BL/6 mouse. *B*, photograph of the *in vitro* rectal preparation with recorded rectal nerve (white arrow) and a 'rake' used to apply graded distension. *C*, electromyographic recording of visceromotor responses to incremental rectal distension in a control C57BL/6 mouse (up to 120 mmHg). *D*, ls/ls mutant mouse, shows characteristic spotted colouring. *E*, rectal preparations from the aganglionic colorectum of ls/ls mice were indistinguishable from control (*B*). *F*, rectal distension up to 120 mmHg did not evoke a measurable visceromotor response in ls/ls mouse, although somatic stimuli (tail pinch, hindlimb pinch, paw pinch and whisker pinch) were effective. *G*, quantification of visceromotor responses to rectal distension in control and ls/ls mice. *H*, distension pressures over 200 mmHg evoked small visceromotor responses in some, but not all, ls/ls mice. *I* and *J*, CGRP immunoreactivity in control mouse colorectum and in aganglionic ls/ls colorectum, respectively. Dense immunoreactivity is present in the myenteric plexus of control mice, but it is significantly reduced in the aganglionic colorectum of ls/ls mice. *K*, CGRP immunoreactivity was significantly reduced in ls/ls mouse rectum, when measured as % of field of view.

colorectum. These are known as muscular, muscular-mucosal, serosal and mucosal afferents (Brierley *et al.* 2004). We found that the muscular and muscular-mucosal afferents responded to distension with low thresholds and wide dynamic ranges which did not saturate across a wide range of stretch amplitudes. Serosal afferents had significantly higher thresholds. This is relevant because visceromotor responses evoked by noxious colorectal distension were consistently activated at distension pressures in the range of 20–40 mmHg. However, serosal afferents had thresholds of 10–20 g circumferential load, which corresponded (using the Young–Laplace law) to intraluminal pressures of 50–100 mmHg. In contrast, low-threshold wide dynamic range fibres had thresholds below 3 g (~15 mmHg). This suggests that low-threshold, wide dynamic range fibres are likely to carry most of the afferent signal involved in visceromotor responses. Thus, high-threshold (serosal) afferents (Song *et al*. 2009) are likely to play a much smaller role in distension-evoked visceromotor responses from the colorectum. Even at maximum stretch (20–40 g which corresponds to 100–200 mmHg using the Young–Laplace law) serosal units contribute only 5% of total stretch-induced firing from the colorectum. Taken together, these findings suggest a major role for rectal low-threshold wide dynamic range mechanoreceptors in the generation of VMRs to colorectal distension.

Exactly how disruption of endothelin-3 signalling causes changes in spinal afferent density and mechanosensitivity remains unclear. Recent studies have shown that family members of glial cell line-derived neurotrophic factor (GDNF), which are known to be essential for migration of

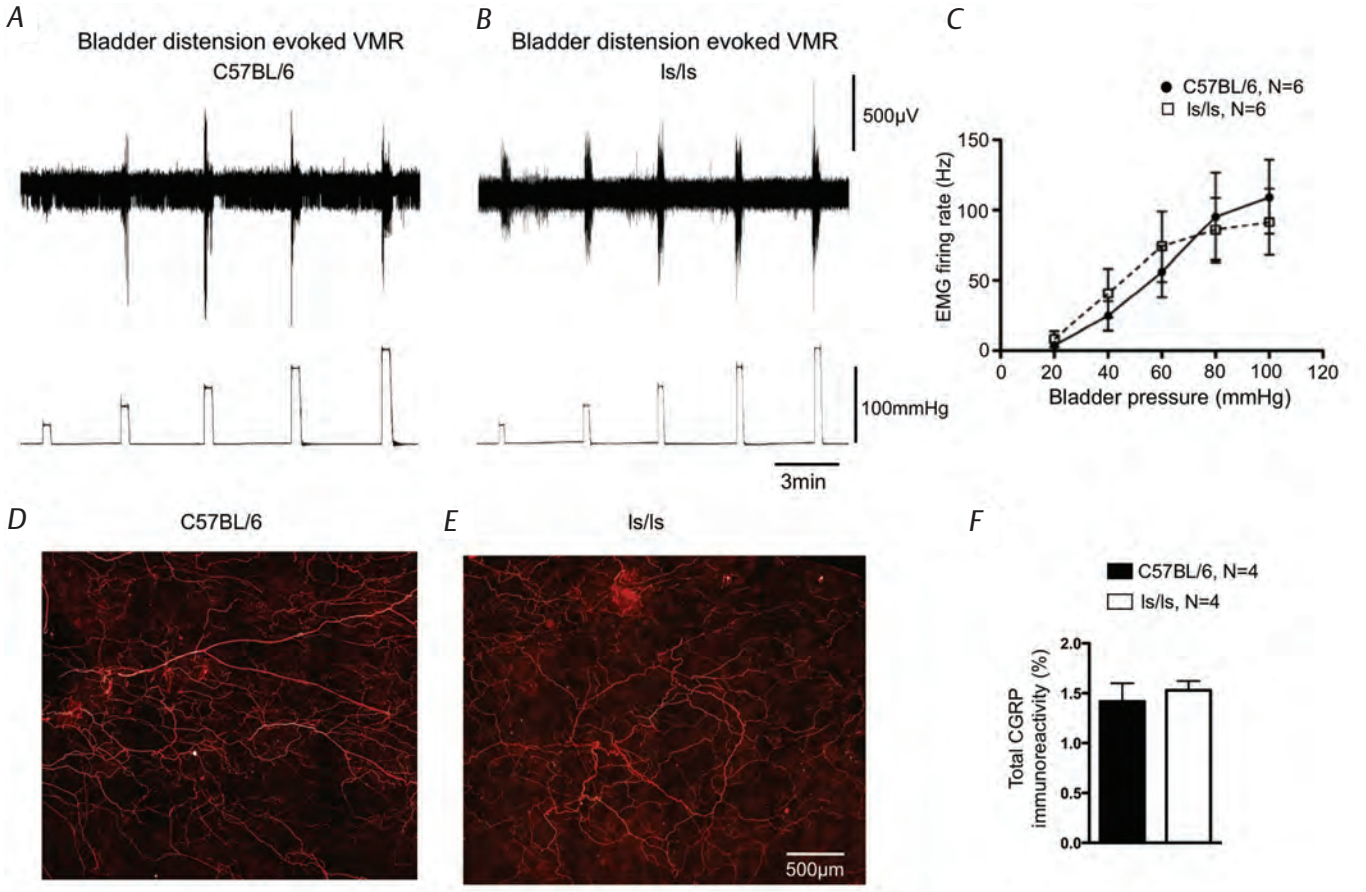


**Figure 2**. Is/Is mice show normal visceromotor responses to bladder distension. *A*, visceromotor responses in control mouse to graded bladder distensions (20–100 mmHg). *B*, similar responses were seen in Is/Is mice and *C*, averaged stimulus–response curves in controls and Is/Is mice did not differ significantly. *D* and *E*, similar CGRP immunoreactivity from spinal afferents innervating the control and Is/Is mouse bladder detrusor muscle. *F*, no statistical difference was found in total density of CGRP immunoreactivity between the bladders of control and Is/Is mice when measured as % of field of view.

the enteric neural crest during development of the enteric nervous system (Heanue & Pachnis, 2007), also play a major role in visceral hypersensitivity and sensitization of muscular and muscular-mucosal colorectal afferents (Tanaka *et al*. 2010). It is intriguing to speculate that endothelin-3 may play a trophic role in the development and/or survival of low-threshold stretch-sensitive afferents involved in rectal nociception.

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### Acknowledgements

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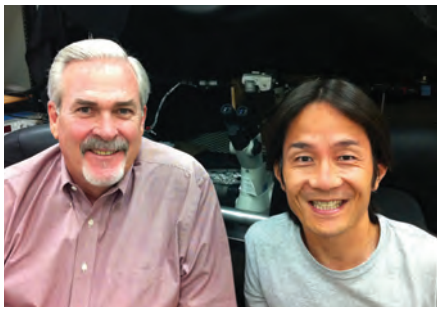
# ‘Fibroblast-like cells’ mediate purinergic neurotransmission in gastrointestinal smooth muscles

Fibroblast-like cells are abundant in smooth muscle tissues, but little is known about the functional role of these cells in normal tissues and their fate in pathophysiological conditions. New genetic animal models now make it possible to isolate fibroblasts from smooth muscle tissues, and physiological and molecular analyses are beginning to reveal the physiological role of these cells in health and disease.

Morphologists have described fibroblasts in smooth muscle tissues for many years, and it has been assumed that these cells are involved in construction and maintenance of the extracellular matrix and in other housekeeping duties. In gastrointestinal (GI) muscles, fibroblasts are not randomly distributed, as might be the case if the cells were involved only in maintenance of the extracellular matrix. In fact, the distribution of fibroblasts is analogous to another type of interstitial cell, interstitial cells of Cajal (ICC), which have important functions such as pacemaker activity, propagation of electrical slow waves, mediation of post-junctional responses to enteric motor neurons, and mediation of responses to stretch (Sanders *et al*. 2010). A well-ordered distribution often predicts specific roles for cells in the function of a tissue.

## Morphology and ultrastructure of fibroblast cells in GI muscles

Initial investigations of interstitial cells of the GI tunica muscularis by Terumasa Komuro with scanning electron microscopy showed flattened cells with many processes in the region of the myenteric plexus, but it was difficult to distinguish between ICC and fibroblast cells with this technique (Komuro, 1989). Transmission electron microscopy (TEM) provided ultrastructural detail and allowed Komuro and others to observe distinct structural differences between ICC and fibroblasts. TEM became the best technique for identifying these cell types in smooth muscle tissues. Well-developed rough endoplasmic reticulum, Golgi and the absence of a basal lamina are among distinguishing characteristics of



Kenton Sanders and Masaaki Kurahashi

fibroblasts. These cells were also clustered around neurons with distances of as little as 50 nm between nerve varicosities and fibroblasts. Fibroblasts also formed gap junctions with each other and with smooth muscle cells. In fact, serial sections showed that fibroblasts formed an electrical bridge between the circular and longitudinal muscle layers, which may explain electrical coupling and coordination between muscle layers.

## Expression of ion channels mediating enteric neurotransmission in fibroblast cells

Fibroblasts were also found to express ion channels that could mediate post-junctional responses to purine neurotransmitters (i.e. small-conductance $Ca^{2+}$-activated $K^+$ channels, SK3). Klemm & Lang (2002) observed SK3 immunoreactivity in the guinea-pig GI tract in cells with distributions similar to ICC. They speculated that $SK3^+$ cells might mediate purinergic responses in GI muscles. $SK3^+$ cells were shown to be $CD34^+$/$Kit^-$ fibroblast-like cells in human and murine GI muscles (Vanderwinden *et al*. 2002). A confusing issue from molecular expression studies, however, was that smooth muscle cells express SK2 channels (Klemm & Lang, 2002), another isoform of small-conductance $Ca^{2+}$-activated $K^+$ channels. Thus, while opening the door to the possibility that cells besides smooth muscle cells might mediate purinergic neurotransmission, expression studies were not able to determine with certainty the cells responsible for inhibitory neural regulation.

## New tools to study fibroblast cells

We were intrigued by the proximity of fibroblast-like cells to enteric nerve terminals and their abundant expression of SK3 channels because we had previously documented a role for ICC in enteric motor neurotransmission (Sanders *et al*. 2010). Until recently, we lacked tools needed to study these cells selectively. Satoshi Iino and his collaborators are credited with providing a key observation that facilitated investigation of the fibroblast cells by showing that these are labelled in GI muscles specifically by antibodies to PDGFRα (Iino *et al*. 2009). $PDGFR\alpha^+$ cells in the tunica muscularis are a population of cells quite distinct from ICC, because double labelling with PDGFRα and Kit antibodies does not co-localize. Iino and colleagues used immuno-electron microscopy to show that $PDGFR\alpha^+$ cells were distinct from ICC, closely associated with neurons in muscle bundles, and possessed ultrastructural features that identified them as fibroblast-like cells (Iino *et al*. 2009). PDGFRα immuno-labelling highlighted the organized anatomical localization of these cells in tissue niches shared by enteric ganglia, processes of motor neurons, tissue macrophages and interstitial cells of Cajal and confirmed expression of SK3 by $PDGFR\alpha^+$ cells. In fact, so similar is the distribution of $PDGFR\alpha^+$ cells and ICC, we chose to refer to these cells

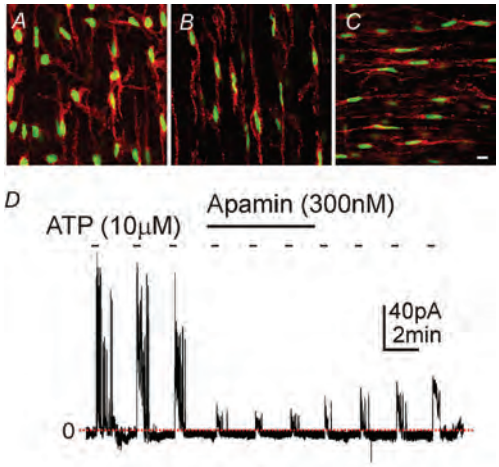



**Figure 1.** Constitutive labelling of PDGFRα⁺ cells with eGFP. *A–C* show green nuclei of cells expressing histone–eGFP fusion protein driven by cell-specific endogenous *Pdgfra* promoter in the region of the myenteric plexus (PDGFRα-MY; *A*) and within the circular (PDGFRα-IM; *B*) and longitudinal (PDGFRα-IM; *C*) muscle layers. Cells are double labelled with antibody against PDGFRα. Cells with green nuclei in cell dispersions were used for patch clamp experiments. *D* shows cell under whole-cell voltage-clamp conditions (holding potential –50 mV). Application of ATP (10 μM) elicited large outward currents that were reduced by apamin (300 nM).

with the same nomenclature used by most investigators to distinguish sub-classes of ICC (i.e. cells with multiple processes found in the region of the myenteric plexus, but outside ganglia, are termed PDGFRα-MY and intramuscular cells found within muscle bundles in close association with the terminals of enteric motor neurons are termed PDGFRα-IM).

Iino's immunohistochemical techniques (Iino *et al*. 2009) also provided unique opportunities to better understand the physiology of these cells. To accomplish this, we used a transgenic animal that was engineered to utilize the endogenous, cell-specific promoters for *Pdgfra* to drive expression of a histone–eGFP fusion protein. Thus, cells that normally express PDGFRα display bright green nuclei due to the constitutive expression of eGFP (Fig. 1*A–C*). These animals provided an opportunity to collect identifiable PDGFRα⁺ cells for molecular expression and physiological studies. When GI muscles from these animals were dispersed with proteolytic enzymes, small round cells with 6.0 pF cell capacitance were identified in the mixed cell populations (Kurahashi *et al*. 2011). It should be noted that PDGFRα⁺ cells are likely to be prevalent in enzymatic dispersions of all smooth muscle tissues, and these cells may be a major component of preparations often referred to (possibly in a manner that is markedly too cavalier) as 'cultured smooth muscle cells' and used widely as models of smooth muscle growth, plasticity and cell signalling.

## A new player in enteric motor neurotransmission

A consistent observation about fibroblast cells in GI muscles is close association with enteric motor neurons. PDGFRα⁺ cells also form gap junctions with neighbouring smooth muscle cells, thus creating a low-resistance electrical pathway between these cells and the smooth

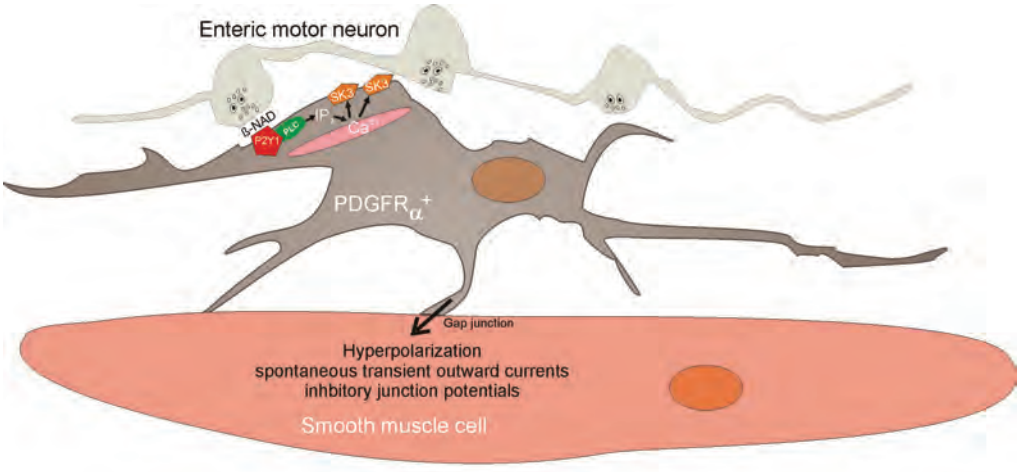



**Figure 2.** Model for role of PDGFRα⁺ cells in GI muscles. PDGFRα⁺ cells are closely associated with varicosities of enteric inhibitory neurons that release purine neurotransmitter when stimulated (β-NAD). PDGFRα⁺ cells express P2Y1 receptors that bind to purine transmitter resulting in liberation of $IP_3$ and release of $Ca^{2+}$ from stores. Localized release of $Ca^{2+}$ activates SK3 channels in the plasma membrane resulting in cell hyperpolarization. PDGFRα⁺ cells are electrically coupled to smooth muscle cells, thus hyperpolarization responses are conducted to smooth muscle, causing purinergic inhibitory junction potentials. PDGFRα⁺ cells also generate spontaneous transient outward currents (STOCs) that, when summed, would produce a net hyperpolarizing influence on the smooth muscle syncytium. Thus, PDGFRα⁺ cells regulate basal excitability of smooth muscle as well as mediating responses to purinergic nerve stimulation.

muscle syncytium. Since PDGFRα$^+$ cells express SK3 channels and a component of post-junctional responses to inhibitory nerve stimulation is blocked by apamin, a potent inhibitor of SK3 channels, we tested the hypothesis that PDGFRα$^+$ cells may mediate purinergic enteric inhibitory responses in GI muscles. Pharmacological studies have also shown that P2Y1 receptors mediate post-junctional purinergic responses in GI muscles, so we tested and confirmed expression of P2Y1 receptors and SK3 channels by PDGFRα$^+$ cells (Kurahashi *et al*. 2011). Under whole-cell voltage-clamp conditions, PDGFRα$^+$ cells generated large-amplitude, $Ca^{2+}$-dependent outward currents in response to P2Y1 agonists (Fig. 1*D*), including β-NAD, a novel purinergic neurotransmitter in the gut (Mutafova-Yambolieva *et al*. 2007). Excised patches of membrane from PDGFRα$^+$ cell exhibited 10 pS, $Ca^{2+}$-sensitive $K^+$ channels consistent with the expression of SK3 by these cells. Under current clamp, the cells generated sharp hyperpolarization responses consistent with the purinergic inhibitory junction potential. Under similar conditions, smooth muscle cells from the same tissues generated little outward current under voltage clamp and net small depolarizations in current clamp. Opening of apamin-sensitive $K^+$ channels (i.e. SK channels) and a rapid hyperpolarization response is a hallmark of purinergic neurotransmission in the gut. Our data demonstrated that smooth muscle cells are incapable of generating purinergic inhibitory junction potentials in the GI tract, but the apparatus to generate hyperpolarization responses is clearly manifest in PDGFRα$^+$ cells that are electrically coupled to smooth muscle cells. It should also be noted that many PDGFRα$^+$ cells generated spontaneous transient outward currents (STOCs) that were apamin sensitive, suggesting that these cells may also contribute to the resting potentials of GI muscles independent of neural input. Thus, it appears that PDGFRα$^+$ cells have at least two major functions in regulating GI motor behaviour (Fig. 2): (i) binding and transduction of purinergic enteric inhibitory neurotransmitter and (ii) regulation of resting membrane potential and control of excitability of the smooth muscle/ICC/PDGFRα$^+$ cell syncytium.

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# How good is spontaneous sequence analysis at measuring baroreflex sensitivity in man?

Spontaneous sequence analysis (SSA) is a widely used but controversial technique to measure sensitivity of the heart period component of the baroreflex in man. The principal controversy concerns whether all the sequences it finds are random or causal relationships between blood pressure and heart period. Evidence indicates that the data it generates are not substantially contaminated by random relationships. SSA therefore appears more useful than previously supposed and as good as (and no worse than) any other technique for measuring baroreflex sensitivity, but could still be improved.

## Introduction

The baroreflex is believed to be an important means of stabilising blood pressure in mammals and has multiple efferent components, including changes in heart rate, stroke volume and peripheral resistance. Systolic (rather than mean or diastolic) blood pressure (sPB) is usually measured as the input, since this represents the greatest dynamic stimulus to baroreceptors. Its heart rate component is the most often studied output, as it is easiest to measure and only this component is considered here. Mechanistically it may make more sense to consider heart period rather than heart rate (its inverse), since the control system actually advances or retards the next heart beat, rather than setting a particular heart rate.

## No agreed gold standard for baroreflex sensitivity measurement.

A major problem in baroreflex sensitivity measurement is the absence of an agreed, absolute gold standard against which to validate all baroreflex sensitivity measurements. There are agreed absolute standards to measure pressure (mmHg) and time (milliseconds). But there is no agreement about how best to provoke the required change in pressure, how big the pressure change should be and over what time the heart period response should be measured. The absence of any accepted validation means there is no means of knowing what the hypothetically correct baroreflex sensitivity value should be when any technique is applied. So if two techniques agree on a baroreflex


Michael Parkes

sensitivity value both could still be wrong. Conversely, if two techniques disagree, we don't know which is right, or which is nearer the hypothetically correct value. Without validation, the next best thing is to establish whether each technique can identify the fundamental properties of the baroreflex in man. Perhaps the simplest fundamental property is the attenuation of the heart period component of the baroreflex by the inspiratory phase of the central respiratory rhythm (Mancia & Mark, 1983).

The first formal studies of the heart period component of the baroreflex in man used systemic injection of pressor or depressor drugs (phenylephrine, angiotensin II or nitroprusside) to cause a change in systolic blood pressure, measured the heart period response and derived a baroreflex sensitivity value in ms $mmHg^{-1}$. This is sometimes called the 'Oxford technique'. There are several reasons why not all accept this as the gold standard. Different drugs produce a different gain value and the gain value also differs (an hysteresis) depending on whether pressor or depressor drugs are used. Possibly both result from all drugs having other effects in addition to changing blood pressure. Furthermore, all apply an external stimulus to provoke the response, hence come up against Heisenberg's Uncertainty Principle. The first proponents of the Oxford technique in man (Smyth *et al*. 1969) observed that the baroreflex was attenuated in inspiration. Indeed in this and later papers they suggested selecting only expiratory data for analysis.

Subsequent studies developed an alternative technique of applying suction or pressure around the neck. By changing arterial pressure in the neck this stimulates or unloads carotid baroreceptors. Again the heart period response is measured and a baroreflex gain value is calculated. This technique too encounters Heisenberg's Uncertainty Principle and also alters only a sub-population of baroreceptors. It too detects inspiratory attenuation.

## What is spontaneous sequence analysis?

An ingenious alternative idea in the 1980s exploited the fact that blood pressure is never constant, even in healthy, resting and recumbent subjects. It was proposed that, if the baroreflex operates continuously, these spontaneous changes in sBP could be taken as the input, and the output could be taken as heart periods at specific times (lags) in relation to the systolic pressure changes. Although initially using arterial catheters to measure pressure, this technique cleverly exploited the availability of servo-controlled sphygmomanometers (such as the FINAPRES) to track arterial pressure in the finger at around 100 Hz. The great attraction of combining SSA with the FINAPRES is that it provides a non-invasive technique (using only spontaneous physiological

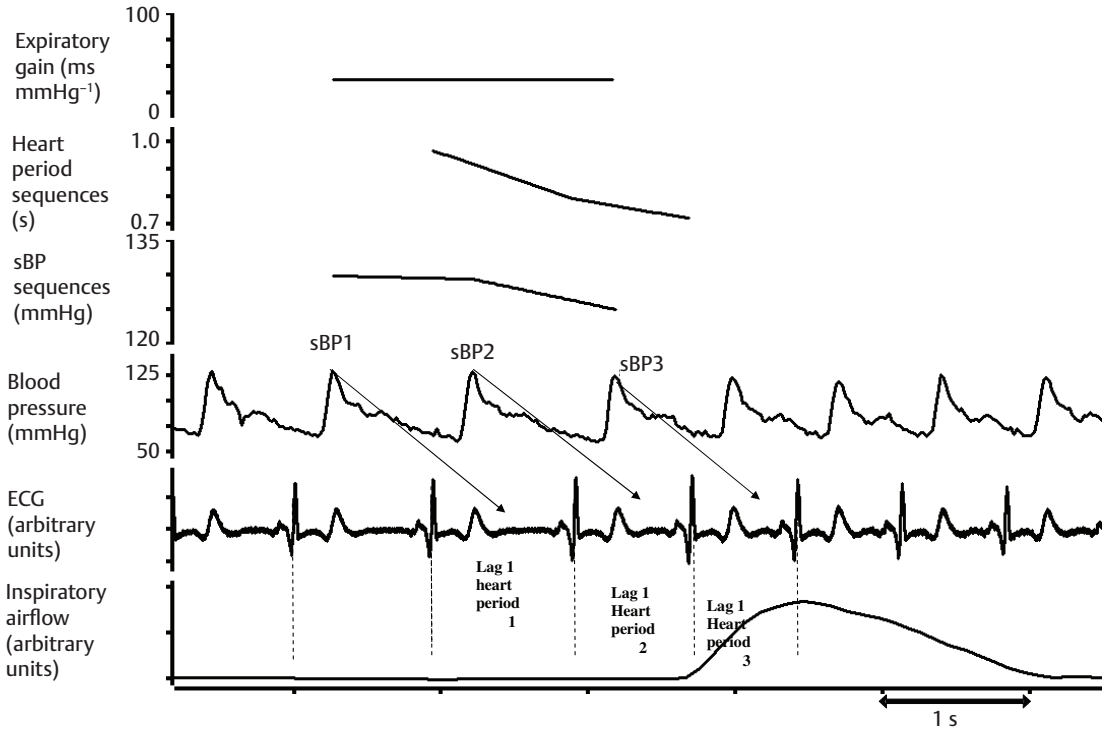


**Figure 1.** Spontaneous sequence analysis of ~6 s of data in one subject showing identification (acceptance) of a 3-beat falling sequence at lag 1 and in expiration. The gain is calculated using the Microsoft Excel formula 'SLOPE(0.969, 0.790, 0.718 s: *vs.*129.9, 129.4, 125.0 mmHg)' = 38 ms mmHg$^{-1}$. The top 3 panels show the convention for drawing a sequence: a line joins the 3 systolic pressures and another joins the corresponding 3 heart periods at lag +1 (their times are arbitrarily assigned to the first beat of their period). The third line shows the expiratory gain value (with its time arbitrarily assigned from its first to third systolic pressure pulse). Reproduced with permission from Hollow *et al*. (2011).

variations in pressure as the input) and therefore does not encounter Heisenberg's Uncertainty Principle. It can also be used to test whether the hysteresis is a drug-induced artefact or a fundamental property of the baroreflex.

All that SSA requires is to record pressure and heart period with sufficient resolution and over a sufficiently long period. A computer programme then goes through the record one beat at a time to find the acceptable sequences. SSA makes the simplistic assumption that each sBP value influences only the next heart period. (More sophisticated analyses of the influence of sBP on multiple successive heart periods have yet to be explored.) For SSA the minimum number of sequential beats over which gain can be measured is three (it being impossible not to draw a straight line through only two data points). Three-beat sequences are also the most common sequence length found and, although longer sequences also occur, they are much less frequent and it is unclear what advantage they offer. Figure 1 shows how the programme searches either for the first three consecutive beats of rising systolic pressure accompanied by three increasing (lengthening) heart periods at a specified lag, or for three falling systolic pressures with three falling (shortening) periods. When found (accepted) their regression slope is calculated to derive the baroreflex sensitivity value in ms mmHg$^{-1}$. If the first three beats do not meet these criteria, the programme then moves along one beat and searches again (with no beat being double counted). Finally, the mean gain value is calculated from as many accepted sequences as are found in the recording period.

## The SSA controversy

As anybody who has tried to publish SSA data knows, use of the SSA technique is still highly controversial. There is no doubt that injection of sufficient drug, or a sufficient change in neck pressure, will cause systolic pressure changes that *must* cause a heart period response. With SSA, however, there is no means of distinguishing random from causal associations between spontaneous pressure changes and the heart period 'responses'. Some believe that so many of these associations must be random that the mean gain value derived by SSA is meaningless. Undoubtedly some spontaneous sequences must be random, so the key questions are 'how many?' and 'do they matter?'.

These can be addressed in a number of ways. The answers appear to be 'not many' and 'probably not!'.

First, if all accepted sequences were random, then sinoaortic denervation should make no difference to the number of accepted sequences found nor to the mean gain value. Such experiments cannot be performed on man, but in several species of unanaesthetised animals sinoaortic denervation does make a large difference: the number of accepted sequences falls by at least

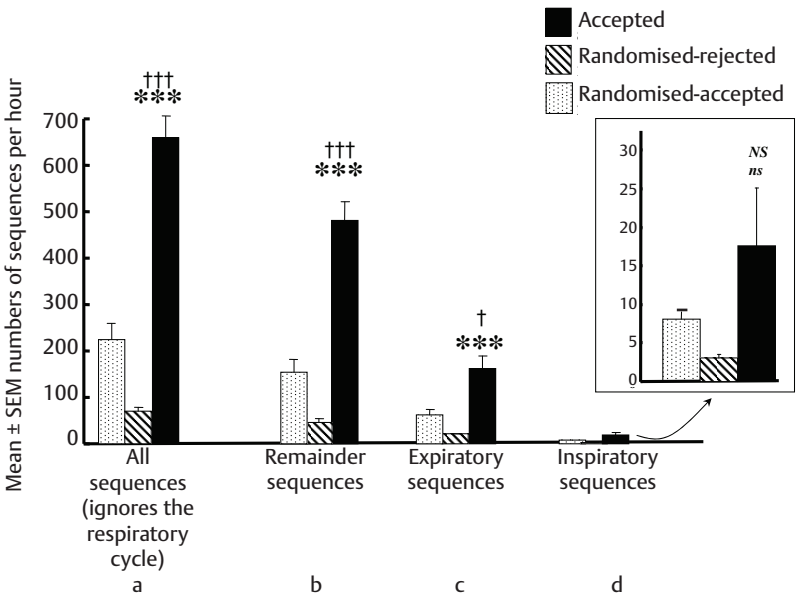


**Figure 2.** Spontaneous sequence analysis finds more sequences than expected by chance. a, the mean number per hour of all accepted sequences in 20 subjects, together with the number of sequences found from the same data if it is randomized and reanalysed (randomized accepted), or if the rejected sequences from the same data are randomized and reanalysed (randomized-rejected). b–d, all data subdivided over the respiratory cycle into expiratory, inspiratory and remainder (spanning both inspiration and expiration) sequences. The inset shows the inspiratory data with an expanded vertical scale). $***P < 0.001$ accepted *vs*. randomized-rejected and NS = $P > 0.05$, †$P < 0.05$, †††$P < 0.001$ accepted *vs*. randomized-accepted, ns = $P > 0.05$, by ANOVA ($F = 63$, $P < 0.001$) and Student's paired *t* tests. Reproduced with permission from Hollow *et al*. (2011).

90% and their mean gain value tends to zero. This confirms that some spontaneous sequences are undoubtedly random, but shows that they form <10% of all sequences and appear to make no important contribution to the overall gain value.

Second, if all accepted sequences were random, then SSA should find no more sequences than expected by chance (i.e. when using a random number generator to redistribute the original pressures and periods over time and then reanalysing this randomized data). A number of studies in man show, however, that SSA finds many more sequences than expected by chance (Fig. 2**)**.

Third, we would expect the sequences rejected by SSA to be random and therefore their mean gain should be zero. We confirm (Fig. 3) that this is the case.

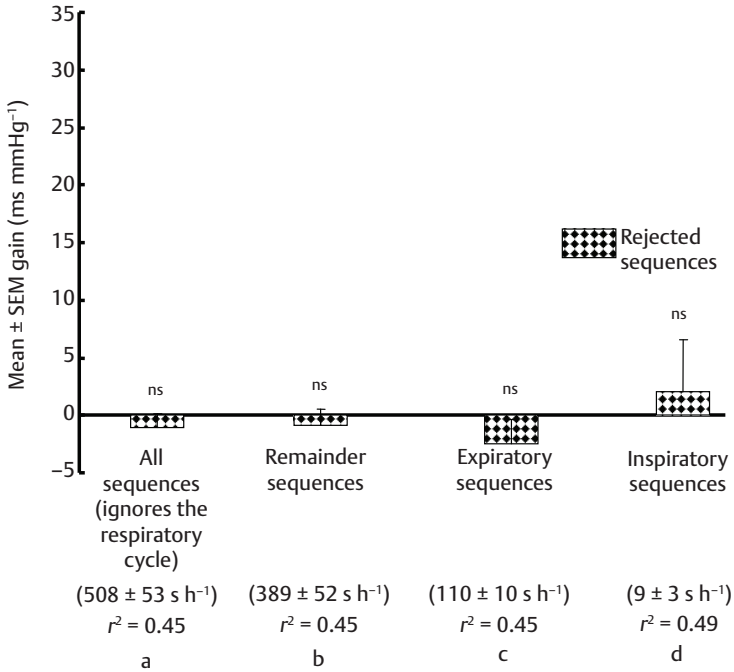


**Figure 3.** Mean gain of rejected sequences is zero. a, mean gain of all rejected sequences in 20 subjects, together with the data subdivided over the respiratory cycle into (b) remainder, (c) expiratory, or (d) inspiratory sequences. Also shown are the number of rejected sequences found per hour and the mean squared correlation coefficient ($r^2$) for each group. (NS = $P > 0.05$ *vs.* zero by paired *t* test). Reproduced with permission from Hollow *et al.* (2011).

Fourth, if all accepted sequences were random, we would not expect SSA to be able to detect the fundamental properties of the baroreflex, such as inspiratory attenuation. We show (Fig. 4) that SSA does detect inspiratory attenuation. So the small number of random sequences does not prevent SSA from detecting this fundamental property of the baroreflex.

## So how good is SSA at measuring baroreflex sensitivity?

The fact that published papers can be selected to show the baroreflex gain value with SSA either agrees or disagrees with those using other techniques is not helpful. This is because we don't know what is the true baroreflex sensitivity value. The best we can say is that all techniques have advantages and disadvantages. SSA now appears better than previously supposed and appears as good as (and no worse than) any other technique.

## Can SSA be improved?

Because of its controversial evolution, numerous fashions have developed in how SSA is carried out, without any being critically evaluated. It is timely to consider whether some standardisation could or should be adopted. For instance, there is no agreement on the minimum time period over which data should be collected, and hence on the minimum number of

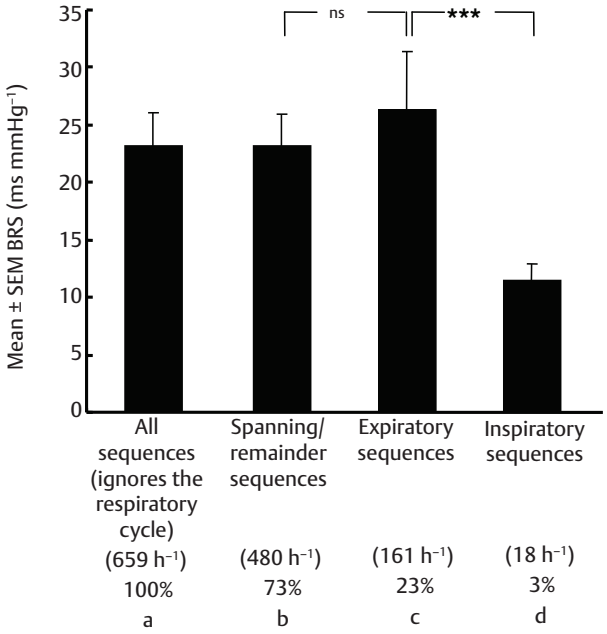


**Figure 4.** Inspiratory attenuation of accepted sequences. a, mean gain, number (also as a percentage) of all accepted 3-beat sequences in 20 subjects in 1 h. b–d, all data subdivided over the respiratory cycle into expiratory, inspiratory and remainder sequences. NS $P > 0.05$, $^{***}P < 0.001$ by ANOVA ($F = 53$, $P < 0.001$) and Student's paired $t$ tests). Reproduced with permission from Hollow *et al.* (2011). **NB 1.** Although the visible mean inspiratory attenuation is 56% (between the 12 subjects with inspiratory sequences *vs.* all 20 with expiratory sequences), the more correct mean attenutation (as used in paired $t$ tests) is 41% (between the same 12 subjects in inspiration and expiration). **NB 2.** Direct comparison of the 'all' *vs.* 'expiratory' means is statistically invalid (because counting the same sequences in both calculations defies the fundamental presumption of independent samples). The 'expiratory' mean is nevertheless significantly higher *vs.* the [all minus expiratory] mean using 2-way ANOVA of individual BRS with subject and expiratory/non-expiratory as the two factors ($F = 6.6$, $P < 0.05$).

sequences that should be used to calculate the mean gain value.

Which lag should be used? Smyth *et al*. (1969) found that the Oxford technique worked best at lag +1, but SSA studies commonly use heart periods either at lag +1 (the next heart period) or lag 0 (the heart period within which the pressure pulse occurs). Figure 5 shows that lag +1 is more sensible. At lag 0 a falling pressure pulse cannot shorten the early part ($x$) of the period (unless you believe in time travel!). Furthermore, a low pressure (sBP1) cannot shorten most ($y$) of the rest of the period because of the finite latency of the baroreflex circuit itself. Thus, falling sequences (~50% of all sequences) can barely shorten heart period at lag 0, whereas rising sequences can still greatly lengthen it. Most SSA studies find no hysteresis (confirming the proposal that hysteresis may depend on the drugs used). SSA studies using lag 0, however, are prone to artefactual hysteresis, because failure to exclude falling sequences will result in accepting ~50% of sequences where it may be physically impossible for low pressure to shorten period.

The effects of breathing could also be taken into account. Failure to exclude attenuated inspiratory sequences reduces the mean baroreflex sensitivity gain value by almost as much as the currently measured effects of ageing, smoking and exercise on baroreflex sensitivity! Alternatively, it might be useful also to measure deliberately the inspiratory attenuation separately, since the vagus nerve in man has negative inotropic as well as negative chronotropic effects on the heart (Lewis *et al.* 2001) and these may be cardio-protective.

SSA techniques also use a wide variety of data filters before accepting sequences: a minimum

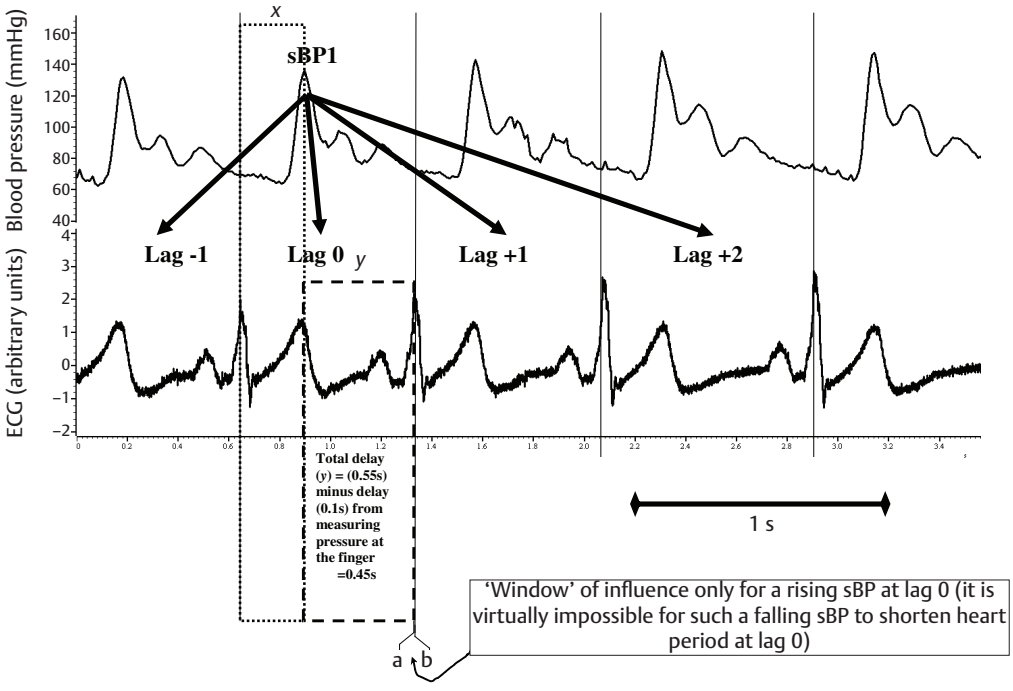


**Figure 5.** Lag +1 is more sensible than lag 0. The figure shows the tiny fraction (between 'a', the end of the baroreflex delay and 'b', the start of the next heart beat) of this particular heart period at lag 0 available for shortening or lengthening by sBP1 via the baroreflex, whereas the whole of this heart period at lag+1 is available. ($x$) and ($y$) indicate those parts of this period that sBP1 cannot influence. **NB.** In ($y$) the baroreflex circuit delay value (0.55 s) is from Borst *et al*. (1985, *Circulation* **65**, 432–434) and the pressure wave delay value at the finger (0.1s) is from Ueda *et al.* (2008, *J Hum Hypertens* **22**, 699–703).

filter size of each pressure or heart period change and a minimum filter size of the correlation coefficient ($r$, or its square, $r^2$) for each slope value. No rationale for such filters has ever been proposed or validated. A number of studies have shown that the $r$ or $r^2$ filter has virtually no effect and, of course, causality cannot be deduced only by correlation. Furthermore, a number of studies have shown that the baroreflex sensitivity gain value depends on which pressure or period filter value is chosen. Yet since we don't know what the true baroreflex sensitivity gain value is, we don't know what filter value(s) to choose. It may, therefore, be safer to filter out only pressure changes smaller than the FINAPRES can measure (0.3 mmHg) and smaller than the smallest heart period that can be resolved (e.g. <1 ms if the ECG is sampled at 2 kHz).

## Conclusions

Over 10 years ago John Dickinson (2001) questioned whether we should still continue to measure baroreflex sensitivity. This question still provokes lively debate. Perhaps the final answer will appear when a simple clinical test is devised that predicts hypertension and heart disease sufficiently in advance to enable effective preventative measures to be put in place. Meanwhile, SSA appears a more useful technique for measuring baroreflex sensitivity than previously supposed, as good as (and no worse than) any other baroreflex measuring technique. But there is still scope for its improvement.

**Michael Parkes**

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# End of an era

Austin Elliott will be stepping down as Editor of *Physiology News* after more than a decade of involvement with the magazine. He succeeded Bill Winlow as Editor after a spell as his Deputy. We, the Editorial Board, are sad to see Austin go; his experience in journalistic science writing is extensive and he fully understands the distinction between the 'hard core' scientific communication required for a journal, where one speaks to a specialist audience, and the more relaxed and open style required for a magazine, with a more varied readership, including non-specialists, and indeed even some non-scientists.

On a personal note I have learnt an awful lot about journalistic science from Austin and over the last few years I have come to regard him not only as a colleague, but also a friend. Austin's emphasis has always been readability - the magazine is often read cover-to-cover and hence needs to maintain the reader's interest throughout. This is quite unlike a journal, where the reader is often interested in a specific article on their own field of expertise. In some ways it is more difficult to produce an informal scientific publication – the criteria for producing an interesting magazine are not simply excellent science and making a valuable contribution to a field.

I am grateful to Austin for his instructive mentoring and the opportunity to watch him ply his editorial craft; he can reduce a verbose and potentially tedious piece into a succinct and far more readable text, and I have often seen him transform an ugly duckling of a script into an elegant piece of prose. Austin's involvement with the magazine stems from a passionate interest in communicating science to a wider audience – he is a keen blogger and active on various fora/blogspots. This genuine desire to make science appealing has been essential for his success as Editor of *Physiology News*.

Under Austin's editorship, the magazine has continued to evolve and thrive as it did during Bill's tenure. He has always been open to new ideas from members of the Editorial Board, and has an intuitive sense of what will work and what will not, no doubt informed by his extensive experience. He has been vocal in trying to instigate a more modern approach to how we publish the magazine – he has been a keen advocate of expanding from only print format to a fully searchable online version, which will hopefully become a reality once the new website comes into existence. Another quality of Austin's which has served the magazine well is his calmness in the face of calamity – whatever disaster might strike, he is completely unflappable.

I would like to thank Austin on behalf of the Editorial Board for his long and dedicated service to the magazine, which he has performed with good humour, just the right degree of democracy and always with great professionalism. We hope that his stepping down from his position as Editor will not mean the end of his written contributions to *Physiology News*. In the meantime, he can also be found writing on his blog – appropriately entitled 'Not ranting... honestly' - over at the Occam's Typewriter blog collective http://occamstypewriter.org/

**Patricia de Winter**

## An unauthorised obituary of my grandfather the geneticist Sir Tarquin Cormorant (FRS)

Tarquin, who rose from obscurity to become one of the towering figures of 20th century genetics research, was born in rural poverty to Bertie and Else Cormorant in 1896. His father, Bertie, was a fantasist and heavy drinker who was involved in a series of business failures, before making a fortune as a second-hand horse trader in the Boer War. Bertie recognised that Tarquin was a precocious child with a cunning intellect and vivid imagination and he invested his money wisely, sending Tarquin to Eton. Although bright academically, Tarquin was expelled in 1911, following a series of incidents, including an unexplained fire. Whilst at Eton, Tarquin developed a keen interest in science and in 1912 he gained a post supervising an archaeological dig in Piltdown, East Sussex. Here, when working alone in the night in treacherous conditions, Tarquin first demonstrated the scientific focus and unique intellectual ingenuity that became a defining characteristic of his career when he personally excavated a skull and lower jawbone of an iconic early human. Although hugely ambitious and driven, Tarquin could be shy and retiring when necessary and he was content to let Charles Dawson take full credit for the discovery. Soon after leaving Piltdown, Tarquin attempted to study at Oxford University, but was initially rejected due to accusations of arson and a poor scholastic record. However, Bertie's financial acumen had enabled him to purchase a peerage and a seat in the House of Lords, from the then Prime Minister, David Lloyd George, and so following an intervention from Downing Street and an unofficial contribution to the construction of a new wine cellar, Tarquin was exempted from military service and admitted to study medicine at Cambridge University. Here Tarquin developed an interest in the role of genetics in the development of personality, the lack of empathy as a defining characteristic of certain personality disorders and forensic medicine. Tarquin finally graduated in Medicine in 1921 with surprisingly poor grades, which he blamed on depression brought about by the death of his college supervisor in an unexplained swimming accident in the River Cam. In 1922, Tarquin married the wealthy but emotionally vulnerable heiress Clarissa Spencer. Their union was turbulent but brief and in 1924, following the death of Clarissa in an unexplained cliff top fall, Tarquin fled to the University of Vienna in Austria complaining of police harassment. Whilst in Vienna, Tarquin developed his obsessive interest in genetics, joining the laboratory of Paul Kammerer. Here he conducted pioneering work on 'epigenetics', conclusively demonstrating that rearing male midwife toads in an aquatic environment induced the development of nuptial pads. It was in Vienna that Tarquin's political conscience was also awakened and he joined one of the fledgling national socialist groups operating in the city, a life choice that Tarquin later claimed to regret. This led to a number of political disagreements with the more classically socialist Paul Kammerer and following *"a piffling argument when some bloody fool suggested that the toads were making inky footprints on the bench"*, Tarquin was asked to leave. Although initially upset, Tarquin was determined to demonstrate the scientific generosity for which he later became famous and he reluctantly allowed Paul Kammerer to take full credit for the discovery.

Tarquin returned to Cambridge and, following the accidental death of his mother and father in a pheasant shoot, inherited a modest £12 million fortune. Having the vision to realise that the world was changing and it was important to ideologically adapt to fit in with the prevailing bourgeois sensibilities of the time, Tarquin joined the Communist Party. Numerous trips to the Soviet Union followed where Tarquin met the young and impressionable Soviet geneticist Trofin Lysenko. Theirs was to prove a sincere and productive collaboration as Tarquin provided the


intellectual and moral framework for a groundbreaking series of studies on vernalisation in cereal crops, a conceptual leap forward in genetics that transformed crop yields in the Ukraine.

The period 1930 to 1960 saw Tarquin contribute a ceaseless flow of innovation to the fields of genetics and personality, undertaking high-profile collaborations with a number of German scientists living in South America and Sir Cyril Burt. He personally spent hundreds of hours analysing data from IQ tests in sets of identical and non-identical twins.

Tarquin was elected as a Fellow of the Royal Society in 1965 and knighted in 1972, but retired in 1982 following a high-profile police investigation into the disappearance of his second wife, Margaret. Aged 108 and in a wheelchair, he was tempted out of retirement to act as a scientific consultant to the University of Seoul, where he again supervised groundbreaking work on the cloning of human stem cells. Characteristically modest, he was again content for another, Professor Hwang Woo Suk, to take full credit for the discovery and he returned home early in 2005 due to ill health.

Professor Tarquin Cormorant (FRS) died 4th October 2011. He is survived by two sons and a daughter.

Josef Cormorant. Ethical advisor to the Serbian government (1995–2000). Present whereabouts unknown.

Sebastian Cormorant. Inventor of the credit default swap.

Brunhilda Cormorant. Jungian psychoanalyst.

**Dr Keith Cormorant**

# The slippery slope to Society Secretary

Years after the events, I've only recently realised that I came close to depriving The Society of not just one, but two of its future Secretaries. The unfortunates involved were David Cotterrell (Meetings, then Committee Secretary 1988–93) and Chris Fry (1995–2002). David, Chris and I were part of the Leicester Mafia that contributed two further Meetings Secretaries (Ron Whittam, 1969–74 and the late Reg Chapman, 1985–91). So here's my side of two stories of what nearly became 'premature Secretaricide'.

David C. was moving house in Leicester one warm summer's day in 1972. I had offered to help. We were taking a heavy, smooth-panelled wardrobe down the flight of steps that finished directly at David's front door. As we negotiated the timber downwards, my grip on the uphill end failed and the wardrobe headed south. Clinging to the downhill end, David became the very image of a Tom & Jerry-style victim. Furniture and physiologist hurtled toward the stair bottom ... and its associated glass front door. With terrific presence of mind, David 'exited stage left' just as the sledge-substitute reached the threshold. The collision, milliseconds later, duly shattered the glass, but David remained intact: and so did the wardrobe ... mostly.

In the summer of 1979, Chris F. had come to join me in Switzerland, where I was working at John McGuigan's lab in Bern. We spent weekends walking and climbing in the wonderful mountains of the Bernese Oberland: here a 'slippery slope' incident might be more readily anticipated. We were heading to the Rottalhutte (Fig.1) – a climbers' hut in the shadow of the Jungfrau (4158 m) and Louwihorn (3779 m) – to overnight there. The last section required a 'contour walk' along a well-trodden pathway across a steep snow slope to reach the hut. At the foot of the 40 deg slope, many metres below us, was a rocky boulder field. But no, we were not roped-up when Chris lost his footing. He shot away downwards, very rapidly and initially on his front. Repeating the Tom & Jerry pose of David C., Chris left two trails of 'claw' marks as he tried, in vain, to arrest his slide. Luckily, he soon bounced over onto his back (and thus his rucksack) as he slid. At least he could see where he was heading, albeit feet first. His trajectory very narrowly missed a huge boulder. At what seemed to me to be a barely survivable speed, Chris reached the abrupt end of the snow-slope, the rock-strewn horizontal. After a moment (that seemed much longer, due to what physiologically illiterate publications unfailingly term a 'surge of adrenaline') Chris shouted up that he was OK. So he had remained intact too. I even had the presence of mind to photograph the trail of (potential) death for Chris' subsequent amusement (Fig. 1). Figure 2 shows that we did at least make it to a decent summit on another weekend.

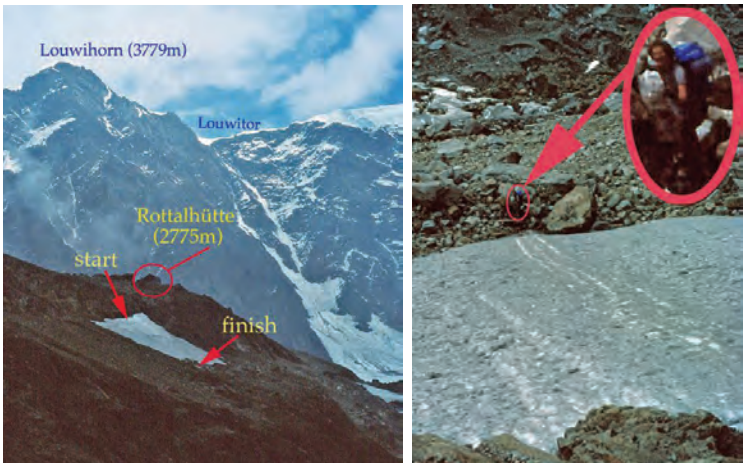



**Figure 1.** Chris Fry – Society Secretary-to-be – counting his lucky stars in Switzerland.

**Figure 2.** Dave Miller and Chris Fry managed at least one Swiss summit without sliding off (on Piz Corvatsch near Piz Murtel).

The Jaunpass near Spitzenegg.

Given the extent of my contributory negligence, and despite our friendship having been, for a few seconds at least, on a poor footing, I've remained on very good terms with Chris and David.

That both went on to distinguished stints as Meetings Secretaries must be entirely coincidental. But one should have anticipated them both being destined for the slippery slopes of life!

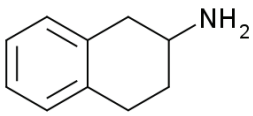
**David Miller**

## 100 years ago in *J Physiol*

**The influence of tetrahydro-β-naphthylamine upon the temperature and respiratory exchange.** N. Mutch & M. S. Pembrey (1911). *J Physiol* **43,** 109–124.

Issues of *J Physiol* from a century ago contain much pharmacology, and biochemistry, as well as physiology. The present paper offers a still-topical example.

The agent tetrahydro-β-naphthylamine is still with us in the scientific literature, but has (rather confusingly) changed its name over the intervening century. Nowadays it goes by either the more chemically systematic name 1,2,3,4-tetrahydronaphthalen-2-amine (THN), or the non-systematic but catchier '2-aminotetralin'. The 2-aminotetralin structure mimics the phenylethylamine skeleton of amphetamines, so it is no surprise that THN has amphetamine-like actions. Later work showed that THN and compounds based on the THN/2-aminotetralin structure have a complex range of effects on aminergic nerve transmission in the CNS. These include sympathomimetic effects, since THN acts as a presynaptic inhibitor of 5-HT and noradrenaline uptake. THN and derivatives also have direct receptor-activating effects, including on dopamine and 5-HT receptors.




THN or 2-aminotetralin

At the time of the paper's publication, biological effects of 2-aminotetralin had been known for over 20 years, being first described in the German literature. Mutch and Pembrey tell us: "The drug has become known chiefly on account of the high temperature which it produces in mammals." Subsequent studies had debated whether this effect stemmed from a change in temperature set-point, as with a fever, or from an increase in heat production via increased muscular activity and breathing, the view that Mutch and Pembrey's experiments support.

Marcus Seymour Pembrey

Mutch and Pembrey tested THN on rabbits. Their description will strike a chord with those who recall lectures on sympathomimetics, CNS stimulants or amphetamine-type drugs, or even on what we now call the 'serotonin syndrome'. The first effect they describe is "an extreme dilatation of the pupil". Subsequently: "The animal soon becomes restless, running about from place to place, sniffing the air and objects around and from time to time giving a vigorous stamp with its hind feet in the way characteristic of wild rabbits when they signal danger. The general behaviour of the animal suggests that it is greatly excited, but is not suffering any distress... The respirations become more rapid and shallow... In some cases there are chewing movements of the jaws..."

Pembrey and Mutch also note occasional unexplained fatalities associated with extreme rises in body temperature, or sometimes with muscular spasms or convulsions. Subsequently they show that THN reverses the sedative effects of shallow anaesthesia, and that spinal lesions only abrogate drug effects below the lesion. Based on all this they conclude that THN stimulates muscular activity and breathing via actions on the brain rather than the spinal cord:

"The action of the drug is upon the central nervous system, upon the higher centres more than the lower; the increased excitability is accompanied by increased muscular movement, spasms or even convulsions."

Marcus Seymour Pembrey (1868–1933) was one of the earliest students to graduate in physiology from Oxford, topping the Physiology class in 1889. Whilst completing clinical medical training he worked in Oxford as a physiology demonstrator under John Burdon Sanderson. He became a physiology lecturer at Charing Cross Hospital (1895) and later at Guy's Hospital Medical School (1899, succeeding Ernest Starling). He spent the rest of his career at Guy's, ultimately becoming Professor of Physiology and FRS.

Scientifically Pembrey's life's work was the regulation of respiration and metabolism, and the related topic of thermoregulation. This began in his time at Oxford, where he and JS Haldane (another of Burdon Sanderson's demonstrators) developed equipment to measure water and $CO_2$ output, and hence respiration, in small animals. This technique was employed in the 1911 paper. Pembrey used the method extensively to study animal thermoregulation, including in hibernators.

In his 34 years at Guy's Pembrey taught physiology to generations of medical students. He was a larger-than-life figure, renowned for his way with a quip and thus in demand to speak at meetings and preside over sundry societies (he served as Phys Soc Treasurer, succeeding Bayliss). Pembrey's splendid Wikipedia entry tells us that 'Old Guy's Men will at once recognize [such] 'Pembrey-isms' as: "Fasting does not make one more spiritual but compels the victim to live upon his own flesh – to become a cannibal"' During World War 1 Pembrey served on the committee that designed the content of army rations, which gave rise to one of his best remembered sayings: "The human or horse works best when well fed, and feeds best when well worked".

Nathan Mutch (1886–1982), born in Manchester, was educated at Cambridge (where he graduated in Physiology in 1907) and at Guy's. He is billed on the 1911 paper as 'Research Scholar of Guy's Hospital'. Mutch went on to a distinguished medical career, becoming consultant physician at Guy's (1918–1946) and head of the hospital's pharmacology department. He was a founding member of the British Pharmacological Society (1931) and an early editor of *Brit J Pharmacol* (1946–50). His most notable work in clinical pharmacology was on magnesium trisilicate as an antacid. When Mutch died at the impressive age of 96, his *Times* obituarist was WDM Paton.

## Evolution: a view from the 21st century

By James A. Shapiro
FT Press Science
£24, 272 pages, hardback
ISBN-10: 0132780933
ISBN-13: 978-0132780933

With a very few exceptions, like Jared Diamond, physiologists have not been active in evolutionary biology for many years. Could that be one more reason for the marginalization, particularly of integrative physiology, during the later part of the 20th century? The theory of evolution is, surely, absolutely central to biology. If you are not part of it, you are peripheral. Moreover, according to the Modern Synthesis (often also called neo-darwinism) the source of change, and hence of speciation, is random mutations. Physiology can have little to say about such a process. At best, through understanding genotype–phenotype relations, we might be able to say which mutations would be beneficial and which therefore would be selected. We investigate the carriers of genes – whole organisms – but, in the Modern Synthesis, genes are the real target of evolution. Other than understanding whether the carrier survives to reproduce, we have little to contribute, and we are certainly irrelevant to the question of the origin of variation. The 'central dogma of molecular biology' has established that the genome is not sensitive to variations in the carrier or the environment.

The compelling reason why physiologists should read Jim Shapiro's book is that this story is wrong. Not just slightly wrong. It is fundamentally wrong. Changes in DNA are not random, and the central dogma does not prohibit changes in DNA in response to stresses in the organism and its environment. Most major changes responsible for new species have not come from chance mutations, but rather from substantial reorganisations of genomes in response to environmental pressures mediated through the integrative ability of organisms to sense these pressures, respond to them, and convey those responses to the genome as an 'organ of the cell', to use Barbara McClintock's famous phrase. In consequence, and contrary to the now out-dated view of my first paragraph, physiology is highly relevant to the evolutionary process. The systems of the organism are the means by which the environment and the organism itself change the genome. Physiology and evolutionary biology therefore urgently need to reconnect. The development of Systems Biology is the interface in which this could happen since it requires an integrative view of genetics. By contrast, the central tenets of neo-darwinism are incompatible not only with a serious role for physiology within evolutionary theory but also with the more recent discoveries in molecular biology.

Shapiro works from within the citadel of molecular biology. He is a bacterial biochemist, but his book and articles extend way beyond the lessons from bacteriology. He freely acknowledges his debt to Barbara McClintock, the discoverer of 'jumping genes', for which she received the Nobel Prize in 1983. He deconstructs the central dogma from a molecular biological viewpoint. So much so that he even eschews use of the word 'gene'. I agree. We can no longer unambiguously define what a gene is. Others have also drawn attention to the need for the Modern Synthesis to be extended or replaced and to the return of forms of what, mistakenly from a historical perspective, is called Lamarckism. But no-one else has documented the molecular biological evidence in such detail and with such an impressive command of the intricacies of genome structure, organisation and dynamics – what Shapiro calls natural genetic engineering. His book has more than 1000 references and, on that basis alone, is a rich resource on such questions, also making for compelling reading. There is also an excellent glossary, a necessary help in a field that is moving so rapidly and coining new terminology with every twist and turn in the story.

I should declare an interest. I was asked to write an endorsement of this book, and was given the usual very brief period of time in which to do so. Fortunately, I had already read some of Shapiro's papers and was able therefore to read and write quite quickly. My endorsement included: "Jim Shapiro has new insights on all the central issues of evolutionary theory. The genome becomes a read–write storage system rather than the sole determinant of heredity. After reading this book, you will find it imperative to see biology as the 21st century is coming to see it." With more time to write this review for *Physiology News*, I read the book again more thoroughly from cover to cover, and did so with increasing enthusiasm. I would not change a single word of my endorsement. Here are a couple of quotations that should surprise those who learnt evolutionary biology more than 15 years ago.

Do proteins evolve one amino acid at a time, as gradual mutation theory would require? Shapiro (p. 95): "The 2001 *Nature* report of the draft human genome contained two important figures illustrating what genome sequencing had taught us about protein evolution. Using transcription factors and chromatin binding proteins as examples, the figures showed that these classes of protein did not evolve one amino acid at a time. Instead, the two classes of protein "shuffled" and "accreted" copies of functional protein segments called domains as eukaryotes progressed from yeast through nematode worms and *Drosophila* flies to mice and human beings. In other words, proteins diversify through a process of acquiring, amplifying, and rearranging coding sequences for subprotein structures that may be dozens or hundreds of amino acids in length."

Can natural selection be responsible for speciation? Shapiro (p. 121): "It

is important to note that selection has never led to formation of a new species, as Darwin postulated." (p. 144): "Selection operates as a purifying but not creative force."

But perhaps the more surprising thing is that these facts have been known for a long time. Shapiro's achievement is to bring great and exhaustive detail to bear on the argument for a revised view of evolution. How then have the lessons been so widely ignored? I suspect that defenders of neo-darwinism would say that bacteriologists have little to tell us about the evolution of higher organisms. It is important to emphasise, therefore, that Shapiro's book also deals extensively with eukaryote evolution. For example, those who argue that way need to read "What makes a man different from a mouse?" (pp. 118–120 of the book). The "genes" (always in quotes in Shapiro's book) are virtually the same. But at least 2 million retrotransposition events separate the two genomes. (These are movements of whole sections of DNA via an RNA intermediate and reverse transcription – one of the first 'breaks' with the original central dogma.)

The main difference therefore lies in regulatory aspects involving parts of the genome about which we still have much to learn: "At present, our understanding of basic principles governing this overall architecture is severely limited, and it certainly deserves to be a prime subject of 21st century research" (p. 118). I would argue that this understanding absolutely requires physiological (functional) insight. Physiology can do that by revealing the higher-level integrative functions that buffer organisms from most changes at the genome level, and by identifying the true regulatory circuits that must involve much more than the genome, and which are inherited along with the DNA. The genome should come to occupy its proper place in the scheme of things as 'the organ of the cell'.

**Denis Noble**

## The Elite Young Athlete

Eds Armstrong N & McManus AM

Karger, vol. 56

£144.70, 205 pages,

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This new volume, *The Elite Young Athlete*, forms part of a long-running series of books in Medicine and Sport Science that stretches back to 1969 when the first volume entitled *Exercise and Altitude* was published. Since this first volume, the editors have aimed to bridge the once much larger gap between medicine and sport, and provide the scientific community with access to the latest findings in sports science and sports medicine. Over the years the series has tackled a wide range of topics including muscle fatigue, exercise biochemistry, movement disorders and biomechanics to name just a few.

The *Elite Young Athlete* focuses on the physiology of young athletes (children and teenagers) as relevant to their training and performance in a variety of sports. Each chapter reads as a stand-alone review on a particular topic, comparing and contrasting published studies in young athletes and discussing the current knowledge in that field. The book begins by covering male and female physiology, in particular the differences in physiological responses and characteristics between males and females both pre-puberty and during and after puberty. Comparisons are made in the physiological responses to exercise between adults and young athletes and important considerations relating to physiological changes associated with puberty that may impact their training or performance are also discussed.

Other topics covered include nutritional considerations specifically relating to this young age group, and the responses of young athletes to endurance, resistance and high-intensity training, both from a performance perspective but also considering safety aspects and long-term health impact of strenuous training regimes on the young developing body. Additional important health and medical aspects are also discussed in other chapters on environmental factors and temperature regulation, overtraining, injuries and sudden cardiac death in young athletes.

One theme that came through in many of the chapters is that in comparison to exercise physiology in adult populations, much less research exists in this age group in terms of athletic performance, training effects and underlying physiology. In line with the increases in paediatric exercise physiology research in recent decades, this book clearly presents the growing evidence that the physiological responses to exercise and training differ with age, maturation status and sex, and emphasises that information on performance and training gleaned from adult studies cannot simply be applied to youth populations.

In each chapter these issues are discussed by drawing together and presenting evidence from published studies. The strengths and limitations of the extant published studies concerning youth athletes are also examined in an intelligent manner, presenting the authors' conclusions but also allowing the reader to form their own opinions from the data presented.

This book is a really nice addition to this long-running series, and the organisation into stand-alone reviews on each topic makes it easy to focus on each aspect in turn. Reading each chapter felt very much like reading a published scientific review, which has advantages but in some instances I did feel a sense of information overload and so found it easiest to read in sections rather than in one go. Extensive bibliographies at the end of each chapter make it easy to be able to find individual research publications for further information, which makes this a valuable reference book for researchers who may wish to read

more and peruse the primary data from the studies presented in the text.

Overall this book covers an important area of exercise physiology and sports medicine, and presented a lot of information in a well-organised and thorough manner. In line with the aims of the editors for this series, the book reads more like a detailed scientific review than a textbook, and this, combined with the fairly high price tag, makes this book most suitable for specialists in this field rather than the more casual reader.

**Samantha Passey**

### BBC National Short Story Awards

In 2005, the National Short Story Prize was launched. This year, Alison MacLeod was a runner-up for her story entitled *The Heart of Denis Noble*, the fictionalised 'eureka moment' of Denis Noble. See his *Living History* article on p. 11 for more details and also go to www.audiogo.co.uk/short-story-award to hear all the stories.



## Dear *Physiology News* Editor

I enjoyed reading the reports of '*I'm a Scientist Get me Out of Here*' by Emily Robinson and Mark Burnley (*PN* **84** Autumn issue). Having also participated in the event – coming 3rd in the Cobalt Zone where I was up against an astronomer (who emerged victorious), a plant biologist, a physicist and a philosopher – I can concur that it is both addictive and a fantastic way to increase your public engagement. It illustrated to me that there are loads of schoolchildren who are curious, keen to learn and who, given the chance, do think deeply about science-related matters.

Having mentioned on my on-line profile that I was a physiologist, there was ample opportunity to advertise our speciality (Q: "what does a physiologist study?") and The Physiological Society. I often directed students to the learning resources in the Education section of The Society's webpage (www.physoc.org/education). This came in handy when having to answer blunt questions such as "do you kill/poison animals?". Maybe I dallied for too long in carefully framing my answer. By the time I had finished logging my lengthy response on the website I noticed that my Zone buddies had already posted answers such as "I look at stars so don't need to kill animals but I don't know how I'd feel about it in any case" to "I work on plants so don't need to touch animals". I might have lost the fluffy vote but it was nonetheless a worthwhile exercise to engage the school students at an early stage in the complex issues around this.

As Emily and Mark mentioned, the questions could surprise you. The most viewed answers in our zone were in response to "Do you believe in God? If not would the loss of a family member affect your ambitions?" which was linked to another query "Is religious belief incompatible with being a scientist?". Again, I took care answering this question but my line of "as scientists we try not to promote theories that we cannot test" might have lost the faith vote.

However, a long-time research collaborator might have hit upon the real reason I didn't reach the final vote. When I mentioned to her that I was by some considerable margin the oldest of the Cobalt Zone participants – all the others being under the age of 25 which I passed in the 1980s – she remarked "you should have used a profile photograph from twenty years ago".

Seriously though, I add my enthusiasm for this event to that of Emily and Mark and encourage physiologists (of all ages) to participate in forthcoming versions. It's great fun.

**Michael Taggart**
Newcastle University

# The Physiological Society Inaugural International Prize Lecture in Beijing and Shanghai, China

I was delighted to receive The Physiological Society's International Prize Lecture for 2011, which I delivered at six medical schools in Beijing and Shanghai, China during 17–25 May 2011. My lecture was entitled *Impaired redox signaling in fetal endothelial cells in pre-eclampsia and gestational diabetes: epigenetic programming of vascular disease*?

I departed for Beijing on 16 May and returned to London after a busy but rewarding series of lectures and meetings with both university staff and postgraduates interested in PhD and postdoctoral training in the UK. My first lecture on 17 May was to colleagues in the Department of Physiology & Pathophysiology, Peking University Health Sciences Center, Beijing, where my host was my close friend and colleague Xian Wang, the Vice Chancellor for Education. Here, I met with graduate students and postdocs at the Office of International Cooperation of Peking University, where Lei Zhang (Associate Director) and Weiwei Du (Programme Office) facilitated a discussion about PhD training opportunities in the UK.

On 18 May I was taken to Tsinghua University, Beijing and shown around the research laboratories by my host Feng-Lin Sun (Assistant Dean of the School of Medicine) who then introduced me to Bo Hong (Vice Dean of School of Medicine) and Xiaoling Liu (Director of PhD Programmes). Following a useful discussion about potential PhD opportunities and exchanges with universities in London and other UK universities, I met graduate students interested in postgraduate training in the UK.

I met with staff from the Institute of Basic Medical Sciences, Peking Union Medical College, Beijing on 19 May, and my host Ji-Min Cao (Department of Physiology) showed me around their old original medical school campus. The medical college is affiliated to Tsinghua Medical School. Over an informal dinner, I briefed graduate students about research opportunities in the UK.

Professor Huirong Liu (centre) and group at Capital Medical University, Beijing.

Friday 20 May began with a memorable visit to the Temple of Heaven coordinated by Anna and Yukii. As my host and close friend Xiao-Ming Wang (Vice President of Capital University and President of the Chinese Association of Physiological Sciences – CAPS) was away, Huirong Liu (Director of the Department of Physiology & Pathophysiology) kindly coordinated my visit and arranged my meetings with colleagues and graduate students of the School of Basic Medical Sciences, Capital Medical University, Beijing.

I departed for Shanghai on Sunday 22 May and was delighted to meet up with Yun Wang (Peking University Health Sciences Center) who played such an integral role in coordinating the Joint Beijing Physiological Sciences Meeting in 2008. In Shanghai I was met by students who kindly took me for dinner in the Shanghai Tower from which I had an outstanding view of the Bund, along the Huangpu River, that once housed numerous banks and trading houses from the UK, France, United States, Italy, Russia, Germany, Japan, the Netherlands and Belgium. My first lecture in Shanghai was to colleagues from Fudan Medical School and my hosts Lan Ma (Changjiang Professor and Director of the Institute of Brain Science & Pharmacology Research Center, Vice President of CAPS) and Yichun Zhu (Department of Physiology) welcomed me and arranged for a meeting with colleagues and graduates, which was followed by a wonderful reunion dinner with friends from Fudan University that I had met during planning meetings for the Joint Beijing Physiological Sciences Meeting in 2008. Amongst the 'surprise' guests was Tai Yao, a long-standing friend and the former President of CAPS.

My final lecture was given to colleagues from the Medical School of Shanghai Jiaotong University on 24 May, where Jing Yi (Deputy Dean of the Faculty of Basic Medical Sciences) arranged for a meeting with graduate students. Later I visited the Shanghai Museum, which provides visitors with a unique overview of the history of Shanghai and the numerous external influences that the city endured over many decades.

Another highlight of my trip was meeting up with my former PhD students Meihua He and Xinghua Cheng and my 'adopted' PhD student Nan Chen, who all returned to Peking University. We visited the Olympic Park from where I was able to peer from hills in the park straight through the city to Tiananmen Square. In the evening, I was treated to a Chinese floor show and excellent dinner in a restaurant where I had dined previously with Marty Franks, David Adams and Prem Kumar in 2006 and 2008.

Many of the colleagues I met at these six medical schools spent significant periods of their research career abroad, based in the USA or UK. All were welcoming and interested in forging stronger links with The Physiological Society and our journals. I would like to formally thank The Society and CAPS, my very generous hosts in Beijing and Shanghai and would like to extend my best wishes to all those that I met but whose names I could not include in this brief report.

Research in physiology and pathophysiology is thriving in China, and I look forward to Chinese physiologists and their younger research staff joining us at the forthcoming IUPS Congress in Birmingham in July 2013.

**Giovanni E. Mann**
King's College London

## Society Representatives

The Society has 75 Representatives across the world who have an important role in helping us communicate and engage with our Members. These Representatives are enthusiastic about advancing the science of physiology and promoting it to the public. They co-ordinate several schemes and support and encourage undergraduates with an interest in physiology.

In September we held a meeting to which all Representatives were invited. This meeting aimed to strengthen the relationship between The Society and its Representatives, provide information and support about what they do, and talk specifically about policy issues at higher education institutions (HEIs).

We met at the Wellcome Trust headquarters on Euston Road, London. Representatives came from England, Scotland and Wales while Frank Mojiminiyi, from Usman Danfodio University, Sokoto, Nigeria, contributed a valuable international perspective to the meeting.

Chief Executive Philip Wright opened the meeting by welcoming everyone. He gave an update on The Society's activities and then handed over to Louise Crane, Outreach Manager, who is now the main point of contact for Representatives at The Society.

Louise led the first two sessions of the meeting. The first explored the role of the Representatives. This led to discussions about the decline of physiology departments and dispersion of physiologists, which makes the role of the Representative more challenging. The importance of raising awareness of physiology was stressed and we agreed that winners of the Undergraduate Prize for Physiology should be lauded more highly at their university – perhaps with an awards ceremony. Not quite the Oscars, but something that allows their fellow students and academic staff to recognise their achievement.

The second session presented new initiatives that Representatives can help The Society with. Louise explained the aims of the new Outreach Strategy, which was recently approved by the Education and Outreach Committee. Outreach, as part of the wider discipline of public engagement, can be used to build communities of non-scientific audiences that have an understanding and appreciation of physiology. We hope it will inspire new generations of physiologists and will ultimately help to raise the profile of The Society. Louise will work with Representatives to help support our Members in carrying out these activities.

Next year, Louise, along with other Society staff including Philip Wright, will be visiting a dozen universities to meet with Representatives and Members. This will build upon the relationships already developed and will be an opportunity for Members to talk with staff about any relevant activities and take part in public engagement and media workshops.

The afternoon focused on policy, with an introduction from Jeremy Ward, Chair of the Policy Committee, that explained what policy is and how The Society carries out work in this important area. Michelle Brook, Policy Manager, then led a discussion that covered many areas of concern, including a decline in the number of physiology courses. It was suggested that the Education and Teaching Theme could carry out a survey to review physiology degree courses and the number of students who take these programmes. This will

Frank Mojiminiyi, Society Representative at Usman Danfodio University, Sokoto, Nigeria.

enable a better understanding of the current landscape.

Other topics that were raised included difficulties surrounding university practicals, accreditation of degree courses and the Research Excellence Framework (REF). These discussions will inform the policy work that Michelle engages with. We will also be taking forward the suggestion that The Society should engage more with senior staff at HEIs to raise the profile of physiology, The Society and its Representatives.

Thank you to all the Representatives who came to the meeting, and Judy Harris from the Policy Committee who also attended. A more detailed report on the presentations, issues discussed and outcomes can be found on our website, along with a list of Society Representatives. If there is no Representative at your university, please consider becoming one yourself and contact Louise Crane (lcrane@physoc.org) to put yourself forward.

Representatives and Jeremy Ward at the meeting.

# Understanding Life

FOCUS ON PHYSIOLOGY

## The Physiological Society's new educational website for schools

We are delighted to announce the launch of our new educational website for schools and further education colleges, at www.understanding-life.org

Aimed at both students and teachers, the *Understanding Life* website provides support for the teaching and learning of physiology, primarily at ages 11–19. This includes:

- **An introduction to physiology, focusing on some of its key areas.** At present, there is a focus on *Sport*, one of the major disciplines within physiology. Future areas of focus planned are *Ageing* and *Comparative Physiology*.
- **Interactive resources designed to enhance physiology within and beyond the 11–19 science curriculum.** These currently include videos, podcasts and links to relevant journal articles. Some resources have been developed by The Society, often in collaboration with other organisations, whilst others have been kindly donated.
- **Details of all The Society's competitions for schools.** The current competition being held is *The Science of Sport: How to Win Gold*, which invites A-level and equivalent students to carry out a research project in an area of sports physiology and present their findings to scientists at The Society's meeting, *The Biomedical Basis of Elite Performance*, on 20 March 2012 in London.
- **Information on The Society's outreach activities aimed at schools.** This includes details of activities we provide as part of science fairs/festivals as well as those run by our Members on an *ad hoc* basis and supported through our outreach grant scheme.
- **Information on careers with physiology.** This section contains information on studying physiology at university, the range of different career options that a physiology degree can open up, and the various careers events The Society is involved with.
- **News on the latest physiology-related resources and activities for schools.** In addition to news on The Society's provision for schools, there are updates from other relevant organisations too.

The rich source of physiology expertise from our Members has enabled us to create this website and we would especially like to thank Valerie Gladwell for her contribution to the *Focus on Sport* and *The Science of Sport* competition pages.

Named after The Society's main educational publication, *Understanding Life* is designed to appeal to students and teachers alike. It has a clean and fresh look, incorporating elements of design from the *Understanding Life* publication, which is intended to make the content and navigation clear to all users.

Navigation has been made even more intuitive by the provision of tagging, which enables users to filter content by, for example, age group or topic. By registering on the website, content can automatically be filtered or flagged to your attention according to your preferences. A facility is also available for users to search content using specific key words.

Other features of the site include social network bookmarking, and links to The Society's educational Facebook page (www.facebook.com/understandinglife) and Twitter feed @ThePhySoc. Also integrated within the *News* section is a customised Google Web Element, which displays external web content, highlighting physiology in the news.

The site also provides a means of linking schools with universities across the UK and ROI. If you are a teacher looking for a scientist or you are a scientist hoping to contact a local school, there is a facility in the *Events* section for you to submit your request to The Society. We will then do our best to put you in touch with the relevant person.

Furthermore, teachers can register as *Contacts* of The Society when creating their online account. This allows us to contact you regarding any updates on The Society's recent and forthcoming educational activities and resources.

Feedback so far has been very positive and includes the following from a secondary science teacher:

"*Lovely website. It's vibrant, interesting and has a very modern feel with a sense of fascination to it. Great work!*"

Over time, new content will be developed and added to the website. If you would like to contribute any resources, suggest ideas for new ones or there is an area of the curriculum that you would like support with, please email education@physoc.org

# Young Physiologists' Symposium: Translational physiology: heart and mind, what makes us tick

Bristol, 6 June 2011

Postgraduates and postdoctoral researchers from across the country gathered amongst the lions, penguins and meercats at Bristol Zoo on Monday 6 June for the Young Physiologists' Symposium '*Translational physiology: heart and mind, what makes us tick*'. The theme of the meeting allowed a range of young scientists to come together, from pre-clinical to clinical researchers, to share their findings from bench to bedside.

The delegates met over coffee and pastries on the Clifton Pavilion balcony overlooking the flamingos. The meeting was opened by a series of fantastic translational neuroscience talks. Highlights included novel ion channels in parasitic nematodes and using optogenetics to excite locus coeruleus neurons. Gavin Clowry from Newcastle University closed the session with his fascinating talk on a career's work on the developmental pathway of the human corticospinal motoneuron and cerebral palsy.

After the morning neuroscience session, there was an opportunity for all to explore the Bristol Zoo gardens. However, it was difficult for most to get past the six-month-old lion cubs Jayendra and Kalyana. Everyone returned for the afternoon seminar series on translational cardiovascular research feeling refreshed and ready for more science.

The day progressed with more excellent talks, from stem cells to activation of brain regions controlling heart rate. Saadeh Suleiman closed the meeting with his talk '*Heartache: protection and repair*', which demonstrated the progression of cardiovascular discovery on the bench directly to the bedside within the clinic, even including some rather interesting videos illustrating open heart surgery.

The organising committee, guest speakers and prize winners.

The quality of the talks and posters was exceptionally high, so it was a difficult job for the guest speakers to choose the prize winners. First prize for the talks went to Heather Weir (University of Bristol) with '*The mitochondrial deacetylase SIRT3 is up-regulated in Alzheimer's Disease*'. Second prize was awarded to Victoria Mascetti (University of Cambridge) and third prize to Laura Newell (University of Bristol). Chinedu Udeh (University of Bristol) won the prize for best poster for '*The transcriptional response mediated by glucocorticoid receptor actions – differential effects of corticosterone administration in mouse brain and peripheral tissue*'. Second prize for the posters went to Roger Watkins (University of Bristol) and third prize to Tony Blockeel (University of Bristol).

The poster session.

The evening gave a chance to carry on conversations in a more relaxed atmosphere with a wine reception and over some very generous portions of tiramisu at *Aqua* restaurant.

Thank you to all the delegates who attended, our guest speakers Gavin Clowry and Saadeh Suleiman, and our generous sponsors New England BioLabs, Bioline, Source Bioscience, SARTRE, Abcam, Caltag Medsystems, Bristol University and The Physiological Society, who made the day possible. A note of thanks also goes to all of the hardworking and dedicated committee: Ana Alviar Baquero, Michael Anderson, Louise Harris, Samantha Lane and Emma Mitchell.

**Kate Weatherall**
Chair of the Organising Committee

# Young Physiologists' Symposium: Epithelial Physiology Across Species

## 31 August, Royal Veterinary College (RVC), London

Delegates assembled in anticipation. A vibrant hum of conversation resonated throughout the Camden campus of the Royal Veterinary College. The YPS, hosted by the Urinary Systems Physiology group at the RVC, was underway.

The meeting began with a brief introduction and welcome address, which set the focus for the day. The primary aims of the meeting were twofold: first, to highlight the diverse nature of epithelial studies amongst various species that focus on epithelial physiology and, most importantly, pathophysiology. We believe that the fundamental pathophysiology of particular diseases can be deciphered by investigating similar manifestations across the species spectrum. Second, we hoped that the early career physiologists in attendance would benefit from the informal environment, where they could discuss their research with fellow early-stage researchers and established investigators alike.

Jonathon Elliott (RVC) gave the first expert talk entitled '*Hyperphosphataemia in chronic kidney disease*'. Professor Elliott's stimulating presentation outlined the difficulties of monitoring this condition in feline populations and also highlighted how these studies could be used to further our understanding of this condition in ageing human populations. David Marples (Leeds) gave the next expert talk entitled '*An absorbing question: aquaporins and antidiuresis*'. This talk highlighted the integral role aquaporins play in the maintenance of water balance across a variety of species.

Following a short coffee break, the urinary theme continued with six presentations given by postdoctoral researchers and PhD students. These short communications covered a wide range of urinary topics such as the role of ENaC, P2 receptors and urotensin in the kidney and ATP signalling in the bladder.

The organising committee: (left to right) Rebecca Birch, Toby Scott-Ward, Holly Courtneidge, Alberto Contreras-Sanz, Jessica Mundy, Carol Crawford and Teresa Kennedy-Lydon.

To conclude the morning session Jens Leipziger (Aarhus) gave a talk entitled '*Lessons from the colon inform the renal tubule, and* vice versa'. This intriguing presentation described ion transport of $K^+$ and $Na^+$ in the distal colon and the distal renal tubule – highlighting the similarities of these tubular structures whilst also recounting the intricate experimental techniques employed to extrapolate these findings.

The meeting resumed after lunch with a talk entitled '*Deconstructing lung alveolar stem cells*' by Juan-Jose Ventura (Cambridge). Dr Ventura described the novel techniques used in his lab to grow bronchiolar stem cells to investigate the mediators involoved in the pathophysiology of the lung.

Dr Ventura's talk was followed by six presentations, again given by postdoctoral researchers and PhD students. This session covered a diverse range of physiological topics from respiratory to epidermal with some BLINaC (the elusive brain liver intestine $Na^+$ channel) thrown in for good measure.

Following a short coffee break Robert Kleta (UCL) gave a plenary lecture entitled '*Renal Fanconi syndrome: Why Snoopy is my favourite dog*'. This fascinating presenation described Professor Kleta's work in deciphering the cause of human Faconi syndrome by studying the manifestation of this disease in the Basenji dog breed. By all accounts it was felt that this lecture really captured the essence of the symposium: employing naturally occurring animal models to further our understanding of human diseases. In addition, Snoopy gained many new fans!

The meeting concluded with a presentation of prizes for outstanding oral and poster communications. Congratulations to our 'best talk' winner Silke Haerteis (Erlangen-Nürnberg) and our runner-up, Dominik Wiemuth (Rheinisch-Westfaelische Technische Hochschule (RWTH) Aachen). First prize for the best poster communication went to Anurag Kumar Singh (Hanover Medical School) and the runner-up prize was awarded to Claire Cox (Cambridge).

I would like to thank all members of the RVCs Urinary Systems Physiology group for their help in organising this meeting and Scott Wildman for his generous help in contacting our many expert speakers. I would also like to thank our sponsors (StarLabs, Promega, GT vision, BioLine, RVC Animal Care Trust and The Physiological Society) and a special thank you to Chrissy Stokes at The Physiological Society.

**Teresa Kennedy-Lydon**

Royal Veterinary College, London, UK

# The status and valuation of medical sciences teaching in academic careers: some progress but room for improvement?

In March 2010 the Academy of Medical Sciences (AMS) published a thought-provoking report on the valuation of teaching in academic careers[1]. It summarised publicly available data on institutional teaching policies as well as the outcomes of questionnaires, focus groups and interviews with many higher education staff and concluded that "*urgent attention on the part of government, research funding councils, HEIs and individual academics is needed to restore the status of teaching to its rightful place in UK universities*". In 2009, a collaborative study by the Higher Education Academy and the GENIE CETL[2] had similarly found that "*most academics feel that teaching and learning is important but that it is undervalued*".

The AMS report recommended a number of changes in university policies and practice to raise the status of teaching and teachers. This summer Dave Lewis, Chrissy Stokes and I surveyed Members of The Society to explore progress in these areas. We made an online questionnaire based on the AMS recommendations available to Society representatives throughout the UK, requesting that a single response be returned from each university. The outcomes of the survey were discussed at a lunchtime Teaching Theme workshop at Physiology 2011 (see photo).

## Outcomes of survey

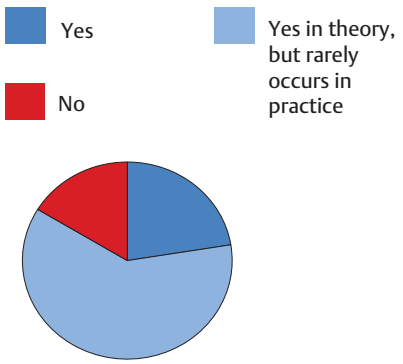
We received responses from 53 of the 81 HEIs balloted, reflecting a wide geographical spread and type of institution. In 45 of these, all academic staff were expected to contribute to teaching. There was a majority view that teacher training for early career academics is useful and relevant, and two thirds of respondents reported that their department/school had a clear strategy for evaluating teaching. However, 60% reported a lack of transparency in the strategy by which teaching is allocated and almost half reported that teaching allocation is not integrated with research activity, administration and staff commitments external to the employing institution. Furthermore, teaching-focused workload models rarely included an allowance for educational scholarship, although this is often cited as a criterion for career progression on the teaching and learning track. It was also interesting to note that, although two-thirds of respondents reported that staff received transparent information about their institution's research income, only one-third reported transparency in relation to teaching income.

There was much disparity in how (and whether) institutions reward and recognise teaching achievements but widespread agreement that, when teaching prizes and fellowships exist, they rarely carry the same prestige or financial value as corresponding research awards. Finally, whilst promotion to professorial level on the basis of achievements in teaching and learning is often theoretically possible, in practice teaching and research achievements are rarely seen as being of equivalent status (see below).

## Discussion at the workshop

The outcomes of the questionnaire provoked lively debate on how The Society might increase its support for teaching and learning and contribute to changing the teaching environment in HE (workshop report and full survey outcomes available from the 'Education and Teaching Theme' website[3]). Suggestions included publishing case studies for individuals who have progressed successfully through a teaching and learning career track; continuing to raise the profile of education and teaching through The Society's Meetings and website; and increasing the number of teaching-focused articles in *Physiology News*. Wider-ranging suggestions including lobbying university senior management to reward, and recognise the importance of, good teaching and considering ways in which The Society might evaluate the quality of physiology teaching in HEIs. All these suggestions are being forwarded to the relevant Society committees for further consideration.

In recent years, The Society has done much to increase the profile of physiology education and teaching. For example, ordinary membership on the basis of teaching resources and/or publications is now possible; the Otto Hutter Physiology Teaching




Responses to the question "At your institution is it possible to be promoted to professor on the basis of achievements in teaching and learning?"

Prize is awarded annually; the Education and Teaching Theme budget is used to fund regular – and well-attended – teaching symposia and workshops; and Council recently approved funding for two teaching fellowship grants each year. Ongoing discussions aim to raise the profile of teaching at Main Meetings.

The wider objective of influencing higher education policy to increase the status of teaching and teachers lies outside The Society's direct influence but the AMS report suggested that "*learned societies and professional bodies can also play an important role in spreading good practice and recognising and rewarding good teachers and mentors*". The current student fees climate and the related increased expectations of students and their parents are raising the stakes in this debate. Will that be sufficient stimulus to reverse the trend, or will teaching continue to be the 'Cinderella' of an academic career?

**Judy Harris**
University of Bristol

[1]*Redressing the balance: the status and valuation of teaching in academic careers in the biomedical sciences* (2010). Academy of Medical Sciences (www.acmedsci.ac.uk/p99puid181.html).

[2]*Reward and recognition in higher education: institutional policies and their implementation* (2009). Higher Education Academy and GENIE CETL (www.heacademy.ac.uk/resources/detail/publications/Reward_and_Recognition_Resource2).

[3]www.physoc.org/site/cms/contentviewarticle.asp?article=988

## New staff at The Society

### Lewis Dean

I joined The Society in October 2011 as Higher Education Officer. In this role I shall be responsible for the wide variety of HE activities that The Society carries out, including, amongst other things, teaching workshops, the Young Physiologists' Symposia scheme and the Philter teaching resource. I am also organising the careers events that we run for university students and early career researchers, many in collaboration with other bioscience learned societies.

After graduating earlier in the year with a PhD in behavioural ecology, investigating cognitive processes in primates, I worked at Sense About Science. There I helped to write public guides to science and worked on campaigns such as the Libel Reform Campaign and Ask for Evidence.

In my spare time I can usually be found listening to Test Match Special, if I am not trying to accomplish that perfect googly.

### Christine Carr

I joined the Society in August 2011 as UK Events & Marketing Manager. Alongside the rest of the Events Team I will be aiding the management and organisation of the upcoming Themed Meetings and Main Meeting over the next 12 months, the preparation of IUPS 2013 and the calendar of events for 2013 and onwards. My other responsibilities include the GL Brown Lecture series and liasing with Theme Leads and the Meetings Committee.

I am very excited to be working at The Physiological Society having gained my MSc in Physiology from Birkbeck College. After briefly working as a science technician I found my way into scientific conference organising via the Biochemical Society, where I worked for 5 years. I then strayed over to the world of biotechnology and then strayed even further, working for the Association for European Transport organising European Transport Conferences for 3 years. Having left the world of trucks, trains and tubes, I am enjoying re-entering the world of physiology (though admit to still being an Eddie Stobart spotter and having named a truck after my mother-in-law).

Outside of work I love going to concerts, finding a good bargain/freebie and warthogs!

### Anne Francis

I joined The Physiological Society's Publications Office in August of this year as Editorial Administrator working both on *The Journal of Physiology* and on *Physiology News*. My main background and interest is music; I sing in the London Bach Choir and teach the piano to a small number of adults and children. Before joining the Publications Office, I worked in an administrative capacity in the higher education sector for a number of years. I look forward to helping anyone with any queries they may have.

# Lab Profiles: Welcome to the Maternal and Fetal Health Research Centre

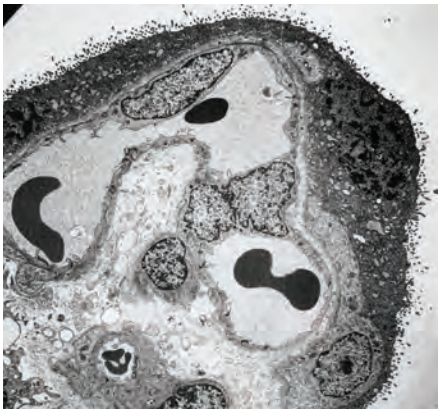
I have recently completed my PhD in the Maternal and Fetal Health Research Centre (MFHRC) at the University of Manchester. MFHRC, headed by Colin Sibley, is located in St Mary's Hospital, Manchester and is the largest pregnancy-based research group in Europe. MFHRC is one of the three Tommy's [Let's Talk Baby]-designated UK Research Centres, which studies placental physiology using a multidisciplinary and translational bench-to-bedside approach. The goal of the centre is to find solutions to pregnancy problems such as stillbirth, fetal growth restriction (FGR) and pre-eclampsia that predispose the fetus to cardiovascular and metabolic complications in later life.

Built around a core team of clinical academics, scientists and midwives, MFHRC mentors promising young scientists at early stages of their career to perform cutting-edge translational research. The Masters of Research (MRes) course in Maternal and Fetal Health run by John Aplin and Rebecca Jones in the Centre is designed to train basic scientists and medical students in many aspects of pregnancy research and transferable skills for future disciplines. MFHRC currently has 12 PhD students and 9 postdoctoral fellows who use a wide range of techniques and methodologies to investigate placental development and function in normal and pathological pregnancies.

Adequate blood flow across the placenta is necessary for the maximal transfer of oxygen and nutrients to the developing baby and a successful pregnancy. A major research focus of MFHRC is to understand how fetoplacental blood flow is controlled in normal pregnancy and dysregulated in pregnancy disease. Paul Brownbill, Tracey Mills, Mark Wareing and Colin Sibley have demonstrated altered

Melissa Brereton

vascular reactivity in placentas of growth-restricted fetuses and of women with pre-eclampsia compared to those of normal pregnancy. Several techniques are used to investigate vascular physiology including perfusion of the organ *in vitro* and wire/pressure myography of isolated vessels. My own research involved developing a technique to isolate smooth muscle cells from the placental blood vessels that primarily determine vascular resistance within the fetoplacental circulation. Using this *in vitro* model, I investigated the expression and function of $K^+$ channels that are crucially important in controlling placental blood flow. It is currently unknown which $K^+$ channel isoforms are localised to fetoplacental vascular smooth muscle cells. Using patch clamp techniques, I demonstrated functional $K^+$ channels including the $Ca^{2+}$-activated $K^+$ channel isoforms $BK_{Ca}$ and $IK_{Ca}$. It is possible that these channels may serve as therapeutic targets to improve blood flow across the placenta in FGR.

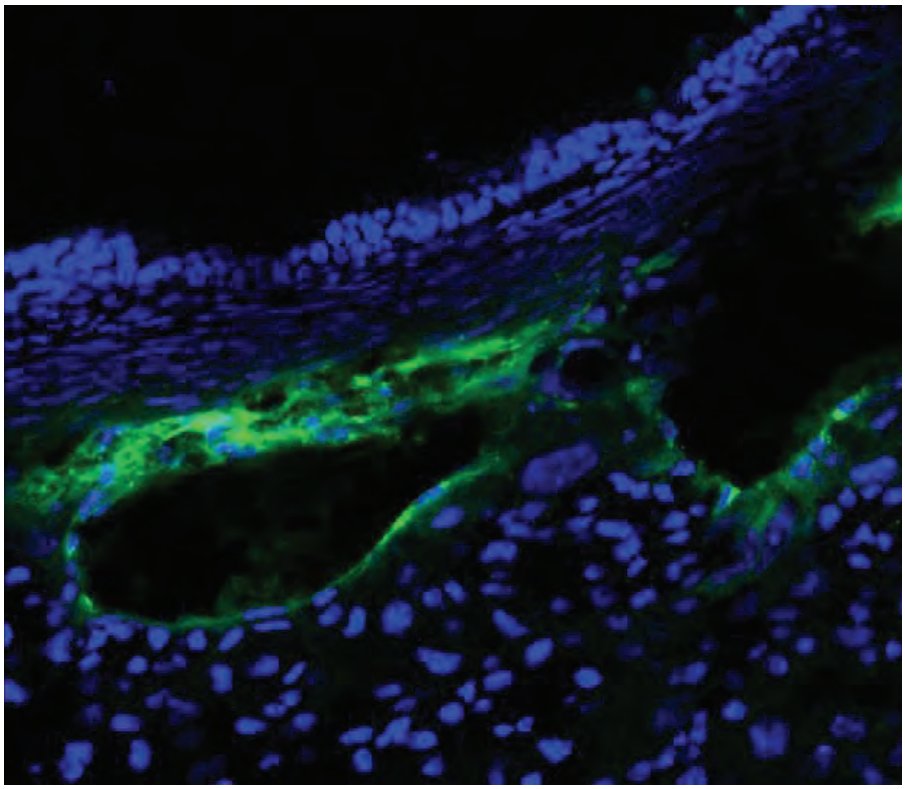


Electron micrograph image of a placental villus. The outermost layer, the syncytiotrophoblast, is the placental exchange epithelia that is bathed in maternal blood and the site of oxygen and nutrient transfer to the fetoplacental capillaries within the villus core. The fetoplacental capillaries contain fetal red blood cells in the lumen and are lined by a single endothelial cell layer. Courtesy of Carolyn Jones.

The physiology/pathophysiology of placental nutrient and ion transport has been another key research interest of MFHRC (Colin Sibley, Sue Greenwood and Jo Glazier). Using a combination of isolated membrane vesicles, cell culture models and placental explants, selective differences have been discovered in the expression and function of nutrient transport proteins/ion channels across the placental exchange epithelium in FGR and pre-eclampsia compared to normal pregnancy. This could contribute to the aetiology of these pregnancy complications. A recent study performed by Andrea Ditchfield in her PhD showed that maternal obesity is associated with reduced placental uptake of taurine, a key nutrient for normal placental and fetal growth, compared to women of ideal weight. This might underlie the increased susceptibility of obese mothers to stillbirth.

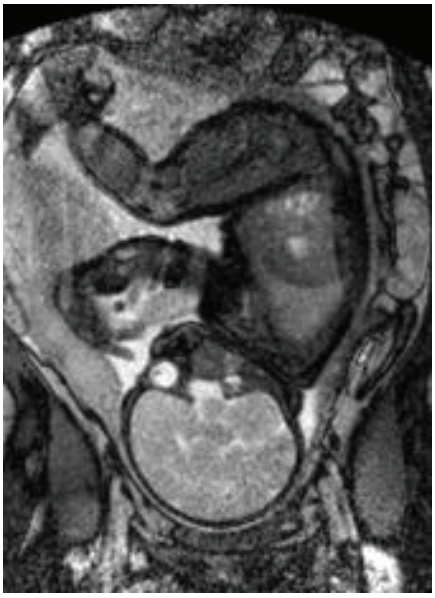
An aim of MFHRC is to gain a greater understanding of placental physiology and pathophysiology through the use of animal models of FGR, pre-eclampsia and gestational diabetes, and to evaluate potential treatments. Funded by an MRC programme grant in collaboration with colleagues at The University of Alberta, Mark Dilworth and Joanna Stanley are assessing the potential of existing therapies to improve fetal growth and development in murine models using a multitude of different approaches including molecular biology, telemetry, metabolomics, ultrasound, small blood vessel myography and radiotracer assessment of nutrient transport. Using animal models of gestational diabetes which demonstrate increased birthweight in common with the human condition, Melissa

Westwood and Raja Nadif are assessing the therapeutic potential of statins in pregnancy to reduce fetal and placental growth. The murine placenta is also an interest of Lynda Harris; her BBSRC David Phillips Research Fellowship aims to identify novel peptides that bind to the surface of the placenta which can be incorporated into liposomes, forming the basis of a targeted delivery system for use in pregnancy. Following intravenous injection to the pregnant mouse of FAM-labelled peptide, Lynda has identified many peptides that bind to the blood vessels and labyrinthine layer of the mouse placenta, which is important in nutrient transport.



FAM-labelled peptide (200 µg) was intravenously injected into a pregnant mouse (embryonic day 17.5) and allowed to circulate for 3 hours. Following cardiac perfusion with saline to remove unbound peptide, peptide binding was visualised by confocal microscopy and shown to localise to the placental blood vessels. Courtesy of Lynda Harris.

Other aspects of research within MFHRC utilise modern molecular biology techniques to investigate how placental growth and development are regulated in early pregnancy. Karen Forbes, with John Aplin and Melissa Westwood, have developed methodologies to introduce short interfering RNA (siRNA) to human placental tissue and investigate the regulation of placental growth by microRNAs. These projects use a combination of bioinformatics, *in situ* hybridisations, placental explant cultures, microarray and microRNA overexpression systems to determine the function of novel microRNAs within growth factor signalling pathways in the placenta. It is hoped that determining the expression profile of microRNAs in normal and pathological pregnancies will identify candidate molecules that can be manipulated to alter growth and development in the placenta.



Scan of a 37-week-old baby used to investigate the role of MRI in understanding fetal and placental physiology. Courtesy of Caroline Wright.

Many of the projects performed in MFHRC are translational and effectively cross the boundary between clinical and scientific research. MFHRC has established the Manchester Placenta Clinic where patients with signs of placental insufficiency, and therefore susceptibility to pregnancy complications, are referred and closely monitored by experienced research midwives and clinical academics. The clinic provides an important service to women with pregnancy complications and is a key addition to MFHRC research. The development of MRI methodologies to monitor placentation across gestation (Ed Johnstone, Caroline Wright and Colin Sibley) is one area that has particularly benefited from the clinic; early research findings indicate that this technique may become an important diagnostic tool for FGR in the future.

Understanding maternal and placental physiological function in normal and pathological pregnancies is important not only for the immediate health and development of the fetus, but for long-term prosperity given the close association between birthweight and susceptibility to cardiovascular and metabolic complications in later life. Integrating the diverse clinical and scientific interests and methodological approaches within MFHRC is key to the success of the Centre. Research will undoubtedly flourish over the coming years as interest in placental physiology increases, and young scientists with fresh ideas and methodologies establish their career within the field.

**Melissa Brereton**
The University of Manchester

# The Journal of Physiology

## JPn

On 1 September 2011 *The Journal of Physiology* published the first of a series of dedicated neuroscience issues (JPn for short). A high proportion of content of *J Physiol* is neuroscience and Editor-in-Chief David Paterson decided that the visibility of *The Journal* within the neuroscience community could be improved through issues dedicated to neuroscience. Volume **589**, issue 17, was the first of these issues and by the time this magazine is published the second issue will also be available.

http://jp.physoc.org/content/589/17.toc
http://jp.physoc.org/content/589/20.toc

The proportion of neuroscience in *The Journal* allows for publication of eight dedicated neuroscience issues per year. The bundling of neuroscience content into dedicated issues inevitably introduces short publication delays but these will be minimised as far as possible and *The Journal* plans to introduce a new fully formatted and copy-edited version of online published articles – the Early View version – to offset the effects of these delays. Each dedicated issue will contain a mix of commentary, review and research content, and a number of sets of neuroscience symposium reviews are also lined up.

The dedicated issues will run as a trial project for a year. It is hoped that they will come to be recognised by the neuroscience community as a source of authoritative information on diverse aspects of the physiology of the brain and nervous system and as first choice for the best work of neuroscientists whose research encompasses physiological mechanisms.

Finally, readers of *Physiology News* may not know that they can receive e-alerts to *J Physiol* content by subject area. To sign up for any of the subject collection alerts go to http://jp.physoc.org/cgi/alerts/collalert

## Vintage physiology

One of the characteristics of great physiologists is their staying power. At Physiology 2011, held in Oxford in July this year David Paterson, the Editor-in-Chief of *The Journal of Physiology*, presented John Coote, Peter Sleight and Jere Mitchell with a special *Journal of Physiology* lapel pin in recognition of their 1971–72 papers on the neural control of the circulation published in *The Journal of Physiology*. These papers [1–4] have become opinion leaders and citation classics, having stood the test of time for 40+ years with more than 1660 citations.

The elite trio, all of them now 'retired' for several years, show no signs of resting on their laurels and slowing down. They retain seemingly limitless enthusiasm for our discipline and each remains extremely active. At the time of writing (August 2011) PubMed listed between them some 23 papers published already in 2011, including two in *The Journal of Physiology*.

Collectively, all our veteran physiologists represent one of The Society's great assets. With a lifetime's experience under their belts and freed from the burden of teaching and administration and the ominous shadows cast by staff cuts and the Research Excellence Framework, their perspective is changed and they bring a different and valuable dynamic to physiology.


*The Journal of Physiology* pin.

## Thelma Lovick

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David Paterson (far left) with (left to right) Peter Sleight, John Coote and Jere Mitchell. Photograph courtesy of Tim Ford.

Experimental Physiology

## New Editors

### Dr James FX Jones

James received his PhD from the University of London in 1993 under the supervision of David Jordan. He is a Senior Lecturer in Physiology at the School of Medicine and Medical Science in University College Dublin. During his early research career he engaged in studies of central autonomic control of the cardiorespiratory system. More recently he has moved his programme of research to the area of autonomic control of the gastrointestinal tract. He has close clinical collaborations and is very active in applied physiological research in the field of faecal incontinence. He has experience of standard electrophysiological tools, multi-electrode arrays and functional magnetic resonance imaging.

### Dr Prem Kumar

Prem received his PhD from the University of Oxford under the direction of Bob Torrance and Piers Nye. He gained postdoctoral experience in fetal and neonatal physiology working with Mark Hanson at the University of Reading before joining the University of Birmingham as a lecturer. He has since held a Lister Institute Research Fellowship and is now a Reader in Cardiorespiratory Physiology in the School of Clinical and Experimental Medicine at Birmingham. His research interests are in the field of chemoreception, with a particular emphasis on carotid body chemotransduction mechanisms in health and disease (particularly chronic obstructive pulmonary disease and sleep apnoea) and in the reflex responses to hypoxia. He has additional interest in the control of breathing during exercise and in the impact of intra-uterine hypoxia upon cardiorespiratory control in the adult.

### Professor Vaughan Macefield

Vaughan is the the Foundation Chair in Integrative Physiology at the School of Medicine, University of Western Sydney, Australia. He completed his PhD in respiratory neurophysiology at the University of New South Wales, and then trained in human neurophysiology in Sydney, Sweden and the US. While his original scientific work involved experimental animals, he now works exclusively on humans, specializing in recording from single nerve fibres via microelectrodes inserted into the peripheral nerves of awake subjects (microneurography). Vaughan is known internationally as a world expert in human sensorimotor and sympathetic control systems: his research examines the encoding of sensory features by specialised mechanoreceptors in skin and muscle, details the firing properties of sympathetic neurones in health and disease, and examines interactions between different physiological systems. In addition, he has been examining changes in control of the sympathetic nervous system following human spinal cord injury, and his research has also extended into the use of brain imaging technology to study the central processing of pain, and to study the central control of blood pressure. Most recently he developed the methodology for concurrent recording of nerve signals in awake human subjects during functional magnetic resonance imaging of the brain, an approach that allows functional identification of areas in the brain involved in the control of blood pressure.

### Professor Jeremy PT Ward

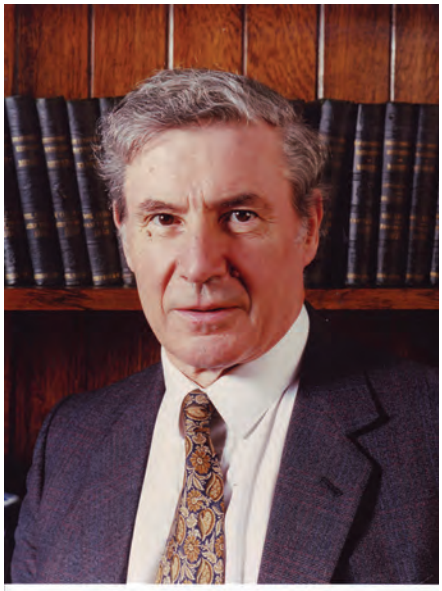
Jeremy is head of the Department of Physiology and Professor of Respiratory Cell Physiology at King's College London. He completed his PhD on potassium homeostasis in cardiac muscle at St Thomas' Hospital Medical School in 1981. His research at King's is currently focused on the cardiovascular and respiratory systems, specifically the signal transduction pathways that lead to activation and contraction of the pulmonary vasculature and airway smooth muscle. He has a particular interest in hypoxic pulmonary vasoconstriction, and the role that reactive oxygen species play in mobilising intracellular $Ca^{2+}$ and activating the protein kinase pathways that underlie smooth muscle calcium sensitisation. He also has a strong interest in asthma and the phenotypic changes that occur in human airway smooth muscle, which result in the hyper-responsiveness and the increased proliferation and secretion of cytokines that are characteristic of this disease.

# John Guy Widdicombe

1925–2011

I feel privileged and somewhat humbled that John's family asked me to write about him for *Physiology News*, following his sad death on 26 August 2011. Although we never collaborated scientifically, I knew John since 1975 when, as a very 'green' lecturer, I joined him at his then embryonic Department of Physiology at St George's Hospital Medical School, London. The new Medical School opened the same year I started and thanks to John's international reputation the department blossomed, new lecturers came in and he attracted scientists from all over the world. The Physiology Department has never seen such vibrant times.

John was born in Barnet, Hertfordshire on 26 December, 1925. His secondary education was at St Alban's School and in 1943 he received a scholarship to study medicine at New College Oxford. He obtained a first class degree in Natural Sciences at Oxford and then graduated in medicine in 1949. He became a house physician for a year at St Bartholomew's Hospital before returning to Oxford in 1950 to take up research. John achieved his DPhil in 1953 as an MRC scholar at the Nuffield Institute for Medical Research. At this time he held the title of Junior Research Fellow at Queen's College Oxford. In 1953 he was conscripted and became an RAF Squadron Leader at Porton Down in the Microbiological Research Establishment. By 1955 he was back to Bart's as a lecturer and then senior lecturer where his research focused on lung mechanics and lung reflexes. In 1960–1961 he was a Visiting Scientist in the Cardiovascular Research Institute in San Francisco, working on the nervous control of breathing and on the regulation of the bronchomotor tone, before returning to Oxford in 1961 as a lecturer in Physiology and Fellow of New College. He continued his work on lung mechanics, the control of breathing and lung reflexes.



John remained in Oxford for 11 years until he took up his post as Professor and Chairman of the new Physiology Department at St George's in 1972 where he was to stay until his 'official retirement'. During his career he was to receive many awards/degrees including his FRCP in London in 1976, an honorary MD from Helsinki University in 2000, nine international medal awards, honorary membership of four international societies and a Life Time Achievement award.

John retired 'officially' in 1992 but remained an Emeritus Professor at St George's until his death and became a visiting honorary scientist at both St Thomas' and Guy's Hospitals in London. In reality though he never retired, working untiringly from home until his untimely death

John was a notable scientist and published over 180 peer-reviewed papers and at least 250 reviews and chapters, as well as his important and well-known monograph, *Respiratory Physiology*. He was also the editor of many multi-author books and symposia and gave uncounted talks and lectures throughout the world. His first paper was published in 1951 (Respiratory and cardiovascular reflexes from the heart and lungs. Dawes GS, Mott JC & Widdicombe JG, *J Physiol* **115**, 258–291) and this year, at the age of 85, he was co-author of at least four papers (to my knowledge!).

John has been described as one of the giants of respiratory physiology over the last 50 years and has deeply influenced our thinking about the anatomy, physiology and pathophysiology of the airways and lungs. He also provided an unparalleled contribution to the understanding and treatment of diseases like asthma and chronic obstructive pulmonary disease.

Although his main scientific interests were respiratory reflexes, he became increasingly interested more specifically in cough reflexes, which became the focus of his later research interests. In fact it is probably true to say that he opened up the whole research field in cough physiology. Indeed, two of his latest contributions to the field were in helping to identify the deflation reflex and contributing to the development of an anti-tussive drug. John was convinced that Aδ fibres play a prominent role in cough mediation. His views on the role of Aδ fibres have now been validated by the results of a new study which demonstrate that the anti-tussive drug VRP7000 markedly inhibits Aδ fibres in the airways. This new drug has now gone through successful clinical trials. In June of this year John attended a 'Cough Symposium' in New York where he remarked that he hoped to see this drug marketed. Sadly, his untimely death meant that this was not to be.

Apart from his major scientific contributions he also contributed to the scientific community as a whole. He was an Editor of *The Journal of Physiology* and *British Journal of Pharmacology* and was also on various other editorial boards. Between 1994 and 1998 he was the President of the British Association for Lung Research and in 1990 he became the Honorary Treasurer of The Physiological Society for 6 years. It was during this time that I became Editor of *Physiology News* and we were both working in a little 'Phys Soc community' at St George's. That is the period we became real friends and he was no longer my revered boss!

John on the river in France.

John was a private person, never arrogant and never known to talk about his achievements, many of which I have discovered whilst writing this article and many of which I have not even mentioned. But he was always a friend and a mentor to his colleagues. What I did discover about him was that he was also a loving and devoted family man. In fact, it was in this role that he became a playwright, writing and producing 3-act plays at Christmas in which he usually cast himself as the grandpa. This meant he was the one member of the cast who did not need to dress up and had very little participation while he orchestrated the whole event. He also loved to entertain (many a good party at his home), loved his house in France and just enjoyed company, good food, good wine and a laugh.

John leaves his wife Margaret and four children, Jonathon, Toby, Marian and Stephen, and five grandchildren. His second son, Hilary, predeceased him. He also leaves a scientific community that, like his family, will miss him.

## Saffron Whitehead

(with grateful contributions from Giovanni Fontana and Clive Page)

**Footnote**

It was sadly ironic that John wrote about himself in his Living History article for the Autumn issue of *Physiology News* (*PN* **84**) this year with the title '*It was the cough that carried him off*'. If you have not already done so it is well worth reading to get John's own personal, funny and self-reflective account of his life (www.physoc.org/magazine).

# John T. Shepherd

1919–2011

John Shepherd was elected a Member of The Society in 1951 and elected to the Committee in 1957. He began his research career in Belfast where he worked with ADM Greenfield measuring blood flow in the hand, using plethysmography. However, as described below by MJ Joyner, the major part of his research was done at the Mayo Clinic in the US.

John Shepherd, MD, a visionary Mayo Clinic physiologist who headed the American Heart Association, served as a NASA adviser and led US scientific exchanges with the Soviet Union during the Cold War, died October 4. He was 92.

Dr Shepherd made major contributions to understanding the regulation of the circulatory system, producing more than 300 scientific publications and four books. He was president of the American Heart Association in 1975–76. He was also a fellow of the Royal College of Physicians, and of the Royal College of Physicians of Ireland.

John received many awards over the years, including honorary degrees from the Universities of Bologna, Ghent and Queen's. He was actively involved with NASA and the National Academy of Sciences, and chaired the Academy's Committee on Space Medicine from 1965 to 1974. During the Cold War, he helped the US space program by working with colleagues in the then-Soviet Union on space physiology.

Dr Shepherd was recognised as a giant in cardiovascular physiology who made fundamental observations about blood pressure regulation in humans and many other elements of cardiovascular control. He was also a visionary leader who engaged in and promoted translational research 30 or 40 years before it was a buzz word at NIH (National Institutes of Health) and in the scientific community,

While John performed cutting-edge scientific work, he was also leading the ongoing transformation of the Mayo Clinic from a group practice to a group practice embedded in a world-class academic medical centre.

He was born May 21, 1919, in Belfast, Northern Ireland, and received his MB, BCh, MChir and MD with honours from Queen's University in Belfast. He completed his internship and residency at the Royal Victoria Hospital in Belfast.

Later, he joined the academic staff at Queen's in the Department of Physiology. In 1953, he was awarded a Fulbright Scholarship to go to the Mayo Clinic for one year to engage in cardiovascular research. The selection of the Mayo Clinic was based on his brother's enthusiasm after reading *The Doctors Mayo* in the late 1940s.

John returned to Northern Ireland but eventually moved to the US in 1957 and joined the Mayo where he spent the rest of his professional career.

He and his three close colleagues in the small Department of Physiology at Queen's University later became deans of medical schools around the world.

At the Mayo Clinic John was Director of Research from 1969 to 1976. He became Director for Education of the Mayo Foundation and Dean of the new Mayo Medical School from 1977 to 1983. This included responsibility for the Mayo Graduate School of Medicine and Mayo School of Health-Related Sciences. From 1983 to 1988, he chaired the Mayo Board of Development and was actively involved in establishment of the Mayo Clinic campus in Jacksonville, Florida. He retired from the Mayo Clinic in 1989. In 2003, he published a memoir, *Inside the Mayo Clinic*.

"As I look back on my fifty years at Mayo Clinic and Foundation, I am astonished at its metamorphosis beyond what William Worrall Mayo, and particularly his sons, Charles Horace Mayo and William James Mayo, first envisioned", Shepherd wrote in his book.

John is survived by his second wife, Marion, a son and a daughter, four step-children, five grandchildren, eight step-grandchildren and a great-grandson.

**MJ Joyner**
Mayo Clinic

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The Society regrets to announce the deaths of Martin Rosenberg, Paul Richardson and Brian Whipp.

Martin died on 15 October. He was elected a Member in 1968 when he was in The Department of Physiology, Basic Medical Sciences, Queen Mary & Westfield College. For many years he was effectively the official photographer for The Society and took a very active part in the recording of Oral Histories. By doing considerable homework before every session, he was able to get the maximum value from each interviewee.

Paul Richardson, who was at St George's Medical School, died on 11 October. He was elected a Member in 1973 and was an Editor for *The Journal of Physiology* from 1974 to 1978.

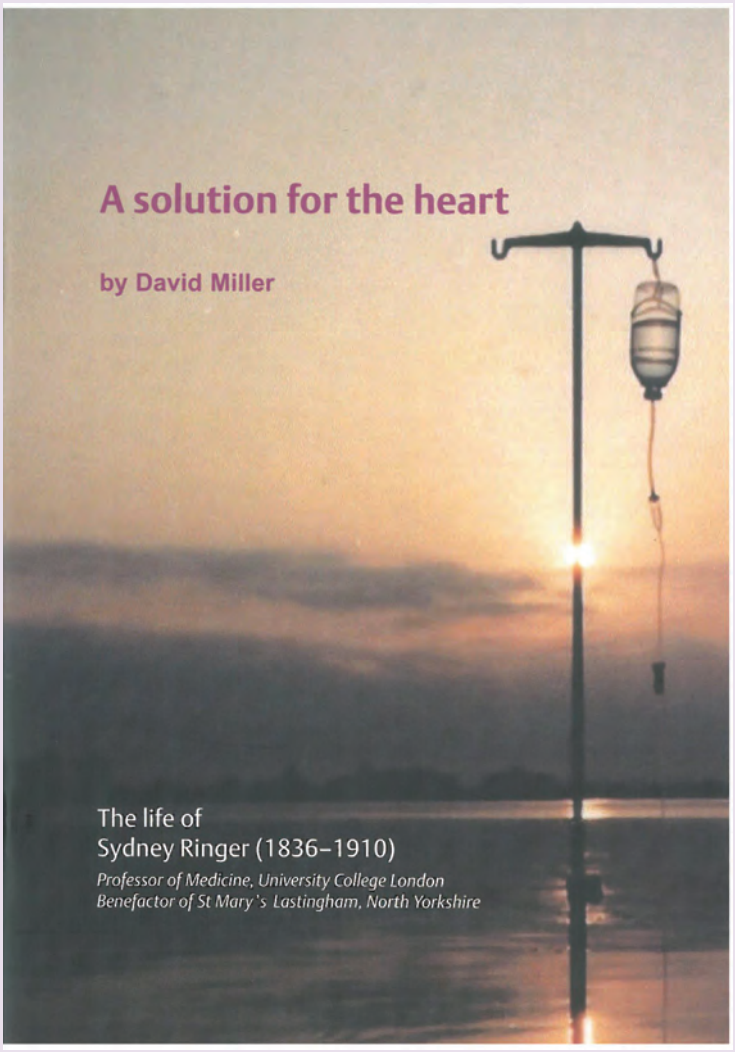
Brian was elected as a Member in 1984. He served on the Committee from 1993 to 1997, and was an Editor on the board of *Experimental Physiology* from 1994 to 2000.

## Paton Prize Bursary

The Paton Prize should not be confused with the Paton Lecture. The Prize was established in 1994 and takes the form of a bursary of up to £1000 to cover travel and incidental expenses. It is open to all Members and Affiliates of The Society, as well as established scientists.

Professor Sir William Paton originated the Prize to encourage the historical study of major ideas and concepts that have shaped modern physiology. The History & Archives Committee administers the Prize and would be delighted to receive applications describing a proposed piece of historical research which could lead to a published paper, a booklet or an article for *Physiology News*.

The Paton Prize was awarded in 2007 to David Miller for research into the life and work of Sydney Ringer.




A solution for the heart: the life of Sydney Ringer (1836–1910)
David Miller (2007)

Applications, in the form of an outline of the proposed work on one side of A4, should be submitted to jberriman@physoc.org by the 16 January 2012 for consideration by the committee. Anyone wanting more details or to talk through an idea is invited to contact the committee chair, Dafydd Walters (dwalters@sgul.ac.uk).

# Announcing...

## NEW Benefit for Society Members!


*Journal published by*
*The International Union of Physiological Sciences*
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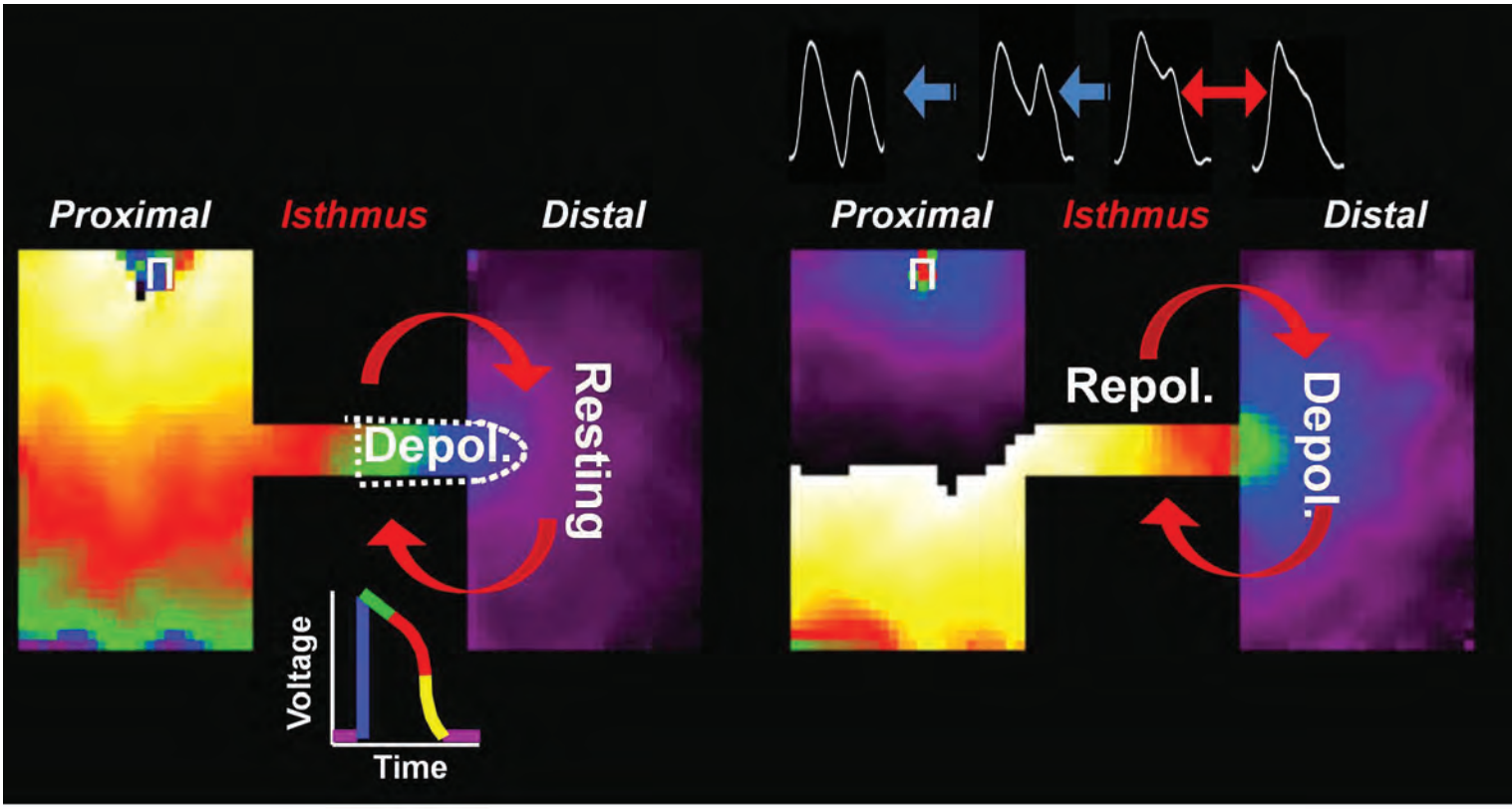


Schematic representation depicting a possible mechanism of re-excitation and reflection at the isthmus (p. 15).

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