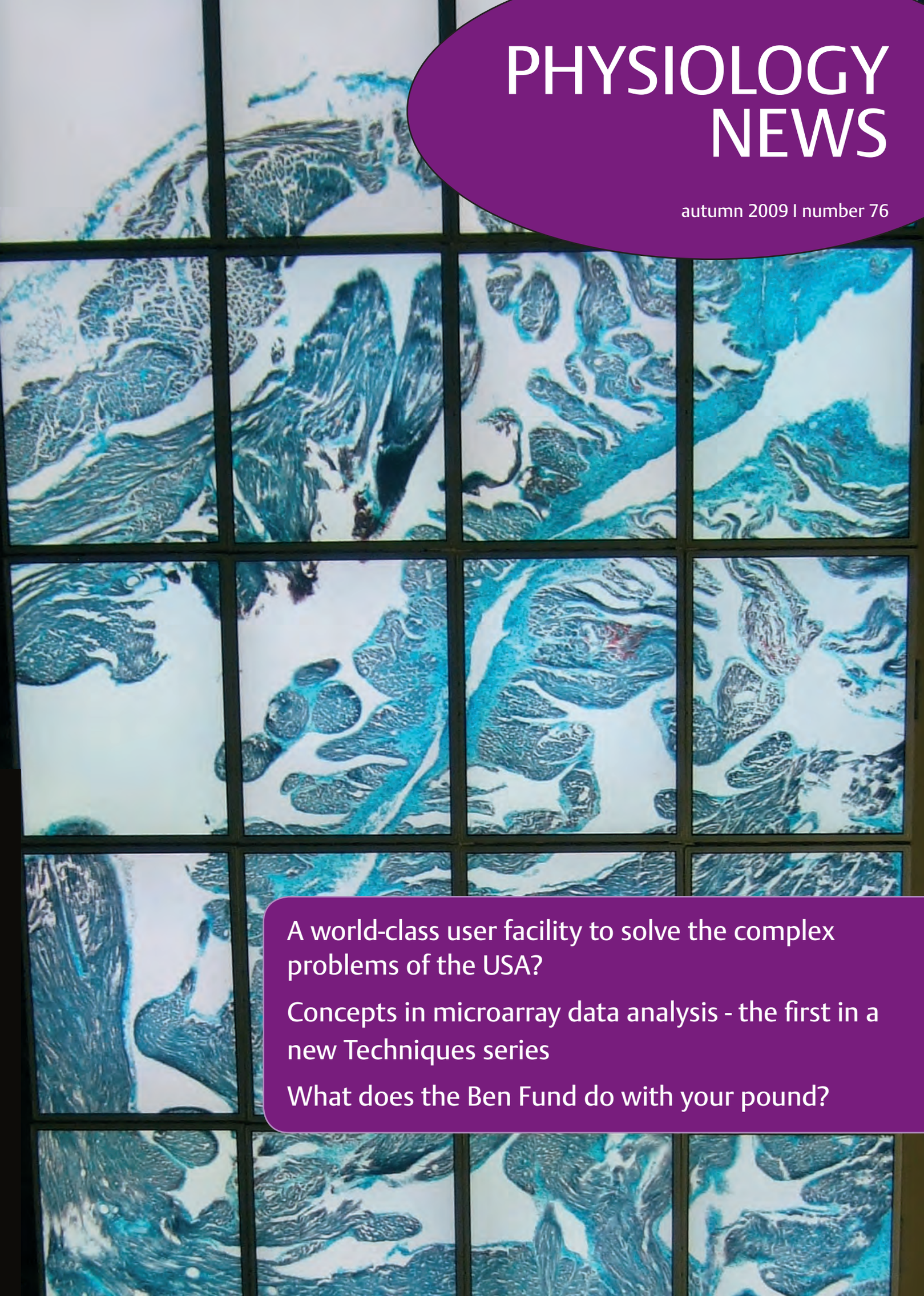

PHYSIOLOGY NEWS

autumn 2009 I number 76

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CELEBRATING OVER 20 YEARS OF INNOVATIONS

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'

Published quarterly by The Physiological Society

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Advancing the science of life

2D histology image shown on a 53.7 megapixel display wall from Goodyer *et al*. p. 18.

PHYSIOLOGY NEWS

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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'.

Physiology News

Deadlines

Letters and articles and all other contributions for inclusion in the Winter 2009 issue, No. 77, should reach the Publications Office (magazine@physoc.org) by **8 October 2009**. Short news items and letters are encouraged, and can usually be included as late copy if space permits.

Suggestions for articles

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

Physiology News online

Physiology News online: www.physoc.org/magazine

Guidelines for contributors

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

Format of articles

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

Length of articles

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

Submission of articles

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

Illustrations and authors' photographs

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

References

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

In this issue

Welcome to the Autumn 2009 *Physiology News*.

Like everyone else in the digital age, scientists are facing problems with 'information overload'. Scientific literature proliferates, and new methods – like microarrays – provide hitherto unimaginable quantities of data. The challenge is to devise new techniques, and adapt old ones, to handle the extra information, as you can see on pp. 18 and 24.

Scientific societies that are charities have a responsibility to provide public benefit – you can find more about this on the 'About Us' page of the Society's website. One way that the Physiological Society addresses this is by a range of activities involving science policy, public engagement and education, and you can read about some of these on pp. 33–36 and p. 40.

Finally, the obituaries record the sad loss of, and pay tribute to, two larger-than-life characters on the UK physiological stage – Professor Philip Poole-Wilson and Air Vice-Marshall Professor John Ernsting CB OBE. Their lives and achievements speak powerfully of the vital and enduring links between lab physiology, medicine and applied human biology.

Austin Elliott
Editor

Caveat lector

Many physiologists will have had the rather depressing experience of looking up one of their papers a few years post-publication, checking the paper's citations – and finding that it has only been cited once or twice. All the more depressing if the only citer is yourself.

All of us, after all, hope our work will be read and appreciated. Similarly, there can be few scientists – if any – who never check the reference lists of a new paper in their own field to see if their work has been cited. If it is depressing not being cited at all, not being cited when one's work is directly relevant is both depressing *and* annoying. And finally, having one's work mis-cited – cited as showing something which it did not – definitely falls into the 'annoying' category.

Accurate and appropriate citation of papers is one of the most basic practices of science, and one of the features that distinguishes science from pseudo-science. People cite the sources for their assertions, so that readers can, if necessary, check the evidence for themselves. But do they?

In a seminal piece of analysis published in the *British Medical Journal* at the beginning of August, Harvard neurologist Steven Greenberg shows how easily selective citation in highly cited works can distort the view of a scientific field, producing an 'apparent consensus' which does not accurately represent the totality of the published evidence[1]. Greenberg's paper, entitled 'How citation distortions create unfounded authority', should be compulsory reading in graduate training programmes. The doctor and science writer Ben Goldacre gives a concise introduction to Greenberg's work on his excellent *Bad Science* blog[2].

Greenberg's main technique is a quantitative analysis of which papers in a research field cite, and are cited by, other papers. Apart from showing which papers are most read (and hence most influential), these citation pattern 'maps' help show how readers actually find their way to the primary experimental work (i.e. via what other sources). They thus map out the way that research papers become well read, or alternatively un-read. Greenberg's chosen example is the expression of β-amyloid protein in skeletal muscle in a condition called inclusion body myositis. He shows that the 10 most cited references in the field promote a uniform view (β-amyloid is part of the injury process in skeletal muscles in the condition) which does not represent the totality of primary experimental evidence (which is equivocal on the point). Greenberg goes on to show that, as expected, primary experimental evidence which supports the view that β-amyloid is expressed is well cited, even if its quality is poor, while literature describing evidence not supporting the hypothesis is cited sparingly, if at all.

Greenberg also demonstrates another phenomenon many scientists will be familiar with – a tendency characterized by an online respondent to Greenberg's article, quoting Lewis Carroll, as 'What I say three times is true'[3]. Greenberg notes how what one paper describes as a 'hypothesis' is transmuted in a paper citing that paper as 'evidence for…'. He also finds examples of the misciting of a primary paper – a largely negative result cited as positive – and subsequent multiple 'secondary citing' of the incorrect (positive) attributed result. He calls this phenomenon 'amplification'.

The tendencies that Greenberg identifies are the more worrying, because we work in an era where the enormous expansion of the scientific literature – an estimated extra 2.5 million peer-reviewed papers a year, with two papers a minute added just to PubMed/Medline – has made it more and more likely that people engage with the literature in the form of review summaries, rather than the original primary papers. Though online full-text access makes it easier than ever before to obtain primary papers, I doubt that the actual reading of them has expanded in direct proportion. The problem, essentially, is that there is too much published science to keep up with – for instance, one review I recently read cites nearly 2500 references[4]. The same review comments wryly on the difficulties this 'literature overload' poses for working scientists:

'… the huge volume of scientific activity has in many ways led to a "balkanisation" of the literature in which scientists deal with the problem of the deluge of published papers by necessarily ignoring most of them.'

The review suggests solutions based on informatics and text mining. But while these may address the information overload, they are unlikely to alter the dangers inherent in reliance on, in effect, Greenberg's 'authority networks'. At bottom, the system is as honest as its practitioners – which means us.

Physiology News has commented many times on the pitfalls for scientists of 'over-selling' their message, whether in press releases, or in the Discussion of papers – and the same goes for review articles. It bears re-stating that a balanced and dispassionate assessment of the evidence for and against various interpretations of the data is the duty that one owes to one's readers. It is also, note, the best insurance against subsequently being proved wrong. If the interpretation is modest and restrained, then any subsequent piece of new information that overturns the interpretation can be put in context – the hypothesis was tenable, and the limits clearly stated, but things subsequently discovered showed it was incorrect. So – a reasonable conclusion, later superceded, as is common in science. 'No harm, no foul'. Now consider the alternative: if the facts have to be tortured to get them to fit a preferred 'partisan' interpretation, subsequent overturning of the interpretation will leave people wondering, at the least, how you got the facts to fit in the first place. These same points apply both to interpreting your own data and to discussing, and citing, that of others.

Scientists, as human beings, inevitably tend to be attached to hypotheses and therefore can allow 'preference' and hunch to creep into their analysis. Pet hypotheses, or hunches, are of course a part of science, because they are part of the make-up of human beings. But the place for them is as idea generators – prompts to do the experiment that will test the idea. Not in the Discussion section of papers, and even less in authoritative reviews. The responsibility of a researcher is to keep 'pet hypothesis' separate from 'rational analysis'.

There is an old adage in the study of history that 'history is written by the winners'. In a similar vein, the history of science shows us many examples where the prominence and influence of proponents, rather than the strength of their arguments, won the day, at least for a time. Greenberg's analysis reminds us that it would be folly to assume modern science has outlived these dangers.

Austin Elliott

References

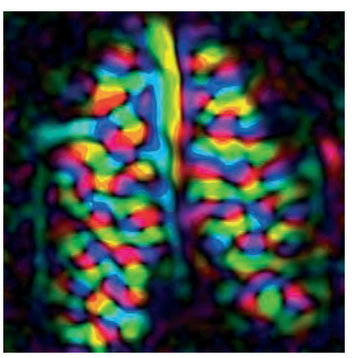
1. Greenberg SA (2009). *BMJ* **339**, b2680.
2. www.badscience.net/2009/08/how-myths-are-made/
3. Goodman NW (2009). *BMJ* Online: www.bmj.com/cgi/eletters/339/jul20_3/b2680#218138
4. Kell DB (2009). *BMC Med Genomics* **2**, 2. doi: 10.1186/1755-8794-2-2

Cellular & Integrative Neuroscience

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

Few areas of neuroscience have been as successful in advancing integrative approaches as sensory and motor physiology. It is therefore timely to have a focused symposium on 'Sensory processing: from transduction to behaviour'. In recent years, significant progress has been made – thanks in part to a number of key technical innovations – at all levels, from transduction in receptor cells to the control of motor output. However, each sensory modality is typically studied in isolation, and most researchers limit their study to one level of processing. This meeting will bring together leading researchers working on all special and somatic senses and at levels of processing ranging from primary receptors to cerebral cortex and beyond. It should therefore appeal to both cellular and systems neuroscientists. Given the broad range of topics, the speakers have been asked to provide a review-style summary of their area of study to bring the audience 'up to speed' before presenting their own latest results. The meeting will consist of five themed half-day sessions, each comprising three or four invited talks as well as related oral and poster communications. The sessions will cover transduction, subcortical and cortical aspects of sensory processing, central control as well as motor integration and behaviour.

Aberdare Hall (dinner venue).



Cardiff University Main Building (top), cat visual cortex orientation map (middle) and Julian Hodge Building (meeting venue).

This 2½-day meeting has been organised by members from Cardiff University and the University of Bristol who have joined forces in the Bristol–Cardiff Neuroscience Collaboration. It will be held at the Cathays Park campus of Cardiff University which recently celebrated its 125th anniversary, having gone through a series of mergers and name changes. The meeting will take place in the modern Julian Hodge Building which is close to the Civic Centre, right at the heart of Cardiff, the capital city of Wales, and only a few minutes walk away from the magnificent Cardiff Castle and the National Museum of Wales. The meeting dinner will be hosted in the fine wood-panelled Staff Dining Club at nearby Aberdare Hall. There are also plenty of hotels, bars and restaurants within a short walk of the venue.

Speakers

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

Helen Kennedy (University of Bristol, UK)

Hugh Matthews (University of Cambridge, UK)

Hiroaki Matsunami (Duke University, Durham, USA)

Maria Fitzgerald (University College London, UK)

Adam Sillito (University College London, UK)

David McAlpine (University College London, UK)

Matteo Carandini (University College London, UK)

Andrew King (University of Oxford, UK)

Irene Tracey (University of Oxford, UK)

Edmund Rolls (Oxford Centre for Computational Neuroscience, UK)

Pieter Roelfsema (Netherlands Institute for Neuroscience, Amsterdam, the Netherlands)

Bridget Lumb (University of Bristol, UK)

Matt Diamond (SISSA, Trieste, Italy)

Peter Brennan (University of Bristol, UK)

Jens Schouenborg (Lund University, Sweden)

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

Daniel Wolpert (University of Cambridge, UK)

Registration and abstract submission opens 28 September 2009.

Please see website for further details.

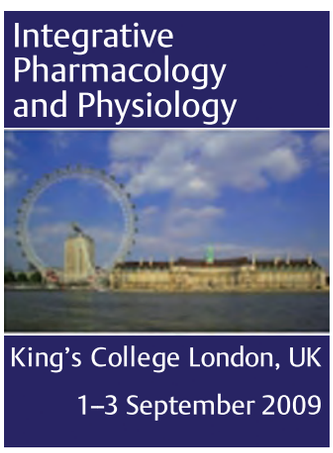
Frank Sengpiel, Richard Apps and Bridget Lumb

Cardiff 2009 Meeting Organisers

7th James Black Conference Joint Meeting of the British Pharmacological Society and The Physiological Society

Integrative Pharmacology and Physiology: translating 'omics' into functional and clinical applications

1–3 September 2009, King's College London, UK



A £250 prize for the best poster presentation by a young researcher (graduate students or newly qualified postdoctoral workers within 5 years of PhD) will be awarded.

For further information:
web: www.bps.ac.uk
email: meetings@bps.ac.uk

Topics covered

Pain, inflammation and injury

Models of cardiovascular and respiratory disease-from bench to bedside

In vivo approaches to studying metabolism

Models of immuno-inflammation and infection: clinical predictive validity

Plenary speakers

Andy Baker (University of Glasgow, UK)

Ian Kimber (University of Manchester, UK)

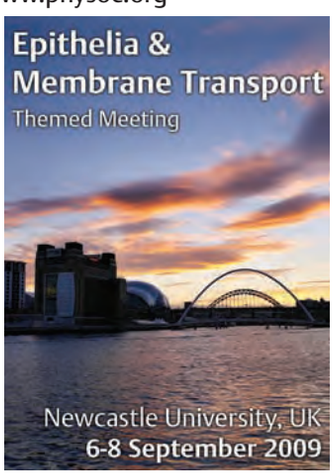
Tony Lam (University of Toronto, Canada)

Steve McMahon (King's College London, UK)

Epithelial form, function and environment

The first Physiological Society Epithelial and Membrane Transport Themed Meeting, 6–8 September 2009, Newcastle University

The organising committee is proud to host this prestigious meeting and to welcome scientists from all over the globe to Newcastle. Newcastle is a thriving cultural city with a strong research focus and an exciting night life. In line with the embracing character of the city the conference dinner comes with a special surprise! Join the meeting, visit Newcastle, all are welcome. Full details are available at www.physoc.org



Development of epithelial structures

Markus Affolter (Basle)
Diane L Barber (San Francisco)
John Sayer (Newcastle)
David Tosh (Bath)
Nick Wright (London)

Physiology and pathophysiology of epithelial solute transport

Peter Agre (Baltimore)
Stefan Broer (Canberra)
Edith Brot-Laroche (Paris)
Dianne Ford (Newcastle)
Yuichi Sugiyama (Tokyo)

Epithelia under stress

James Anderson (Chapel Hill)
Richard Boucher (Chapel Hill)
Tomas Ganz (Los Angeles)
Marshall Montrose (Cincinnati)
Ole Petersen (Liverpool)

Biller Prize Lecture

Gavin Stewart (Dublin)

An introductory workshop to human and clinical physiological techniques

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

Registration opened on 1 August 2009

At the conclusion of the session the participant will be able to:

* Understand the techniques available to measure cerebral blood flow using transcranial doppler, changes in conscious state using EEG, breathing and chemosensitivity in humans

* Understand the limits of human physiology in elucidating the mechanisms interlaying biological control systems

* Examine relationships between molecular, cellular, animal and human physiology

* Have a clear understanding of translational physiology

Techniques demonstrations include:

* Effects of voluntary isocapnic hyperpnoea on respiratory muscle function

* Measurement of dynamic human muscle function

* The pressor response to isometric exercise

* Assessing the effect of muscle vibration on respiratory/skeletal muscle

* The ins and outs of cerebral blood flow measurement using transcranial Doppler

* Measuring changes in conscious state, what happens during sleep? Practical experience using EEG

* Breathless? Can I measure your chemosensitivity?

* To breathe or not to breathe – using non-invasive ventilation

Erratum

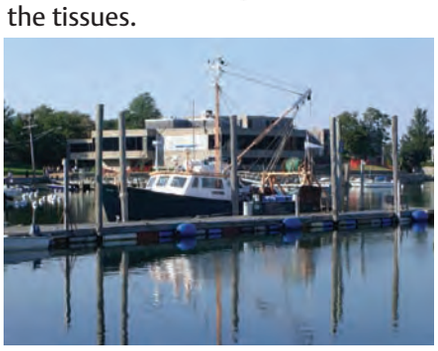
In the article 'In the footsteps of giants' that appeared in the last issue of *Physiology News* (PN75, p. 44), the year that Sir R.A. Fisher obtained a first in Mathematics from Cambridge should have been 1912, and *not* 1922.

Joint International Meeting of The Physiological Society and the Society of General Physiologists

Basic biology and disease of muscle

Welcome to the September 2009 Joint Meeting with the SGP. Woods Hole, 9–13 September 2009

The meeting will cover aspects of cardiac, skeletal and smooth muscle, beginning with the proteins that generate and coordinate the production of force and movement, and end with topics on the maintenance and regeneration of the tissues.



Throughout the presentations, both normal and disease aspects will be highlighted.

Organized by David Eisner and H. Lee Sweeney

Keynote speaker

Kevin Campbell (Iowa City)
The dystrophin complex

Session I. The motor

H. Lee Sweeney (Philadelphia)
Basis of chemo-mechanical transduction by myosin

David Warshaw (Burlington)
Single molecule approaches to studying force generation by myosin

Malcolm Irving (London)
Myosin function in muscle fibers

Session II: Organization, regulation and diseases of the contractile apparatus

Mathias Gautel (London)
The titin-based sarcomeric signaling network

R. John Solaro (Chicago)
Kinase/phosphatase signaling to and from cardiac sarcomeres

Samantha Harris (Davis)
C protein function in cardiac muscle

Kay Davies (Oxford)
Utrophin-based approaches to treating DMD

Elizabeth McNally (Chicago)
Genetic forms of dilated cardiomyopathy

Hugh Watkins (Oxford)
Basic and clinical aspects of contractile protein mutations

Session III: Calcium signaling

Kurt Beam (Denver)
Molecular aspects of excitation–contraction coupling

Susan Hamilton (Houston)
The ryanodine receptor

Clara Franzini-Armstrong (Philadelphia)
Structure / function and excitation–contraction coupling

David Eisner (Manchester)
Cardiac Ca^{2+} cycling in health and arrhythmias

Michael Walsh (Calgary)
Control of contraction in smooth muscle

Session IV: Disease and repair

Mark Nelson (Burlington)
Calcium and blood flow regulation

David Allen (Sydney)
Stretch-induced muscle damage and muscular dystrophy

Susan Wray (Liverpool)
Pathophysiology of uterine smooth muscle

Richard Vaughan-Jones (Oxford)
pH regulation in the heart

Christine Mummery (Leiden)
Heart repair and embryonic stem cells

Gillian Butler-Browne (Oxford)
Skeletal muscle stem cells and therapeutic applications

Society Noticeboard

The Journal of Physiology Symposia 2009

Advances and hold-ups in the study of structure, function and regulation of Cys-loop ligand-gated ion channels
Friday 16 October 2009. At Neuroscience 2009, Chicago, USA.

For full details of this, and other Symposia visit jp.physoc.org

Upcoming deadlines for Scientific Meetings – 2009

For a comprehensive overview visit the website

Integrative pharmacology and physiology: translating 'omics' into functional and clinical applications
7th James Black Conference – Joint Meeting with The British Pharmacological Society (1–3 Sept)

Epithelia & Membrane Transport Themed Meeting
University of Newcastle, UK (6–8 Sept)

Joint International Meeting with the Society of General Physiologists Basic biology and disease of muscle
Woods Hole, MA, USA (9–13 Sept)

Ion channels and receptors in cell physiology
Young Physiologists' Symposia, Leicester (23–24 Sept)

An Introductory Workshop on Human and clinical physiological techniques
King's College London and Imperial College London (10–11 Dec)
Registration opens 1 August

Cellular & Integrative Neuroscience Themed Meeting
Cardiff University, UK (14–16 Dec)
Abstract submission and registration opens on 28 September

2010

Physiology 2010 – University of Manchester (30 June to 2 July)
Abstract submission and registration opens on 1 March 2010

Travel Grants
www.physoc.org/grants
New international grant schemes: www.physoc.org/international

Non-Society meetings

ISAN2009
Manly Pacific Hotel, Manly Beach, Sydney, Australia, 1–4 September 2009
www.isanweb.org

When oxygen is not enough: why is fetal growth decreased at high altitude?

Fetal growth is decreased and infant mortality is increased at high altitude (>2700 m). This means that natural selection is acting against mothers and babies that cannot adapt to high-altitude hypoxia, and perhaps selecting for attributes that protect against chronic hypoxia. Comparison of adapted (native) *versus* non-adapted (migrant) populations is uncovering the mechanisms that regulate fetal growth in an adverse environment and suggesting new avenues for research

Human birth weight is the result of an evolutionary process known as stabilizing selection. In stable environments there is negative selection against the high and low extremes of birth weight, resulting in mean birth weights that approximate the optimal birth weight, i.e. that at which post-natal mortality risk is lowest. Humans are unique among mammalian species in having complications of pregnancy such as preeclampsia and intrauterine growth restriction (IUGR). Amongst other primates, abnormal fetal growth is extremely rare. IUGR costs billions per year in medical and long-term social costs (e.g. physical handicaps, diminished cognitive abilities). These costs accrue throughout life: IUGR infants have an increased risk of developing cardiovascular and metabolic disease later in life (Gluckman *et al.* 2008). It is therefore imperative to find out why a significant number of human pregnancies are afflicted with abnormal fetal growth.

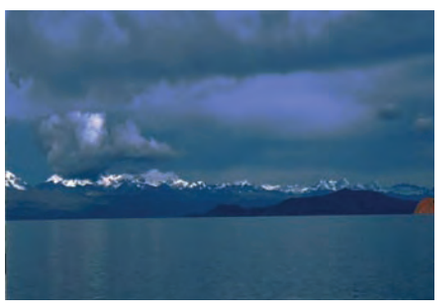
Human residence at high altitude (HA, >2700 m) is a natural experimental model for the study of IUGR. The distribution of birth weights is left-shifted and ~12% of infants are classified as IUGR *versus* 2% at sea level. This disadvantage was first noted in 1639, by Father Antonio de Calancha, who wrote of life in the Andes:

'In Potosi, all children born of Spanish parents died either at birth or within a fortnight thereafter, because the great cold and freezing air would kill them; the mothers used to leave in order to give birth in the neighbouring valleys and until their child was more than a year old the mothers would exile themselves from this city.'

Stacy Zamudio.

Note that it is Spanish parents that are affected, as the altitude-adapted natives did not have a similar problem; indeed there is a gradient of altitude-associated growth restriction such that the longest resident high-altitude populations (e.g. Tibetans) have the least decrement in fetal growth for a given altitude. La Paz, Bolivia, at 3000–4000 m in elevation (left) is one of the most populous high-altitude cities in the world and home to considerable numbers of migrants and natives to HA (below). La Paz draws its native population from all over the 4000 m plateau known as the altiplano (right, Lake Titicaca in the heart of the altiplano).

This renders it ideal for studies of pregnancy physiology to discern what mechanisms cause decreased fetal growth. Or, from a reverse engineering perspective, one can ask, what is it that buffers HA natives from altitude-associated IUGR?



Both experimental animal and human studies have shown that it is lowered oxygen tension (P_{O_2}) rather than nutritional status or other risk factors that is ultimately responsible for the decrease in birth weight. A recent study in chick embryos of low-altitude origin shows unequivocally that the ~38% decrease in fetal oxygen tension is associated with a 45% decrease in fetal growth, which is completely reversed by addition of oxygen (Giussani *et al.* 2007). However, in this experimental model oxygen diffuses through the eggshell directly from the air, whilst mammals have a complicated organ, the placenta, mediating between mother and fetus. In the human we were surprised to find that despite a ~40% reduction in maternal P_{O_2}, there was only a 10% decrease in fetal P_{O_2} in both the adapted natives and recent migrants (Europeans) to HA. However, the altitude-associated fall in birth weight was >16% in migrants *versus* 6% in adapted natives (Postigo *et al.* 2009). Oxygen was not the direct cause, as we found that fetal O_2 delivery was well in excess of fetal O_2 consumption, which was similar across all four groups.

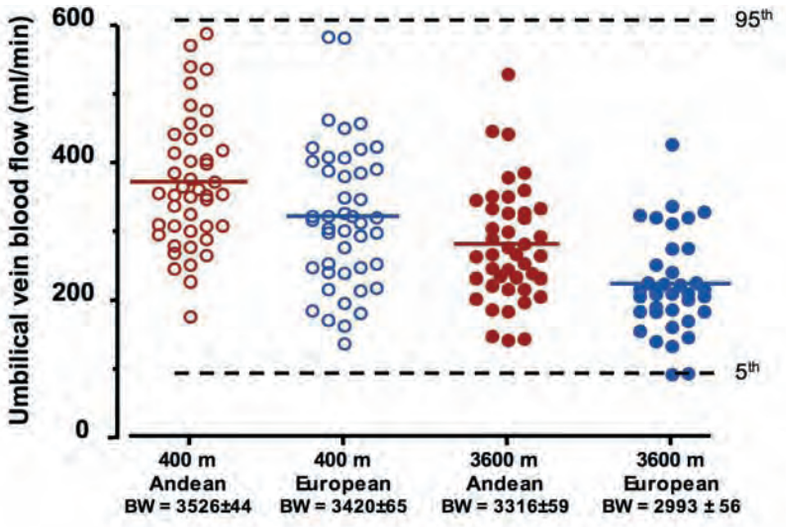


Figure 1. Umbilical vein blood flow in Andians and Europeans at high altitude.

Across numerous mammalian species, blood flow (and hence O_2 delivery) can decrease by as much as 50% before fetal growth suffers (Carter, 1989). Our HA fetuses defended their O_2 supply by increased maternal and fetal oxygen-carrying capacity, increased fetal extraction of O_2, and improved oxygen transfer from mother to fetus and from fetal blood to fetal tissue via the Bohr effect. These adaptations should have compensated for the ~30% fall in fetal blood flow in both Europeans and Andeans at 3600 m (Fig. 1), but it did not.

In theory, reduction in blood flow could diminish flow-mediated transport of glucose and amino acids. However, the distribution of fetal blood flows within each group is well within the 5th–95th percentiles for near-term blood flow according to sea level reference values (Fig. 1) (Acharya *et al.* 2005). The important conclusions in this figure are (1) birth weight (BW) and blood flow are greater in Andeans than Europeans regardless of altitude; and (2) there is considerable overlap in the range of values within each group. The mean values, indicated by the horizontal bar in each scatterplot, range from the 50th to 75th percentile of the sea level reference values. So why is birth weight still reduced, and what accounts for the population difference?

There are several possible answers. First, Native Americans appear to have greater birth weights than Europeans in a variety of environments. Moreover they share ancestral origins with Tibetans. So it is possible that both Tibetans and Andeans are protected against altitude-associated IUGR by virtue of shared genetic ancestry. For example, both Tibetans and Andeans show evidence of increased blood flow mediated via nitric oxide (Beall *et al.* 2001). Second, Tibetans have been at altitude longer and show a smaller decrease in fetal growth than Andeans, thus additional, possibly genetic, adaptations cannot be ruled out. Third, the pattern of increased Andean birth weight at any altitude may reflect a more rapid accommodation to altitude than was previously suspected. Antonio de Calancha reported that for 50 years no Spanish neonate survived at HA, but they surely survived later in the colonial period. A rapid adaptation of this type could be due to epigenetic modification of the placenta. Such changes have already been shown in pregnancy pathologies (Chelbi & Vaiman, 2008) and were invoked by Giussani and colleagues when their experiments in chicks showed that the HA embryos grew bigger when gestated at sea level (Giussani *et al.* 2007). Finally, there is the recently advanced theory of metabolic reprogramming which posits a hypoxia-induced, reversible switch to hypometabolism, which spares oxygen at the cellular level, but at the cost of increased glucose consumption (Aragones *et al.* 2009). This would be consistent with the maintenance of fetal oxygenation at HA, and with our most recent data showing markedly decreased glucose transfer and consumption in the HA fetus. In this last case, decreased fetal growth represents an exquisite balancing act by the placenta to promote oxygen diffusion to the fetus while at the same time limiting glucose delivery and thereby down-regulating fetal growth. It is thus the placenta that may be programming the fetus, which in turn may be responsible for the long-term increase in the risk of chronic disease that IUGR infants incur as a cost of their intrauterine survival.

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Oscillations in brain blood flow revealed by transcranial Doppler

Brain blood flow changes spontaneously with various amplitudes over many time scales. For the most part, oscillations in brain blood flow reflect similar changes in arterial pressure. The dynamic pressure–flow relationship of the cerebral circulation can be assessed using transfer function analysis which may provide important insights into the dynamic control of the cerebral circulation

In this study, transfer function gain (reflecting the strength of association between blood pressure and cerebral blood flow) and phase (reflecting the timing of association) were reduced during acute increases in arterial pressure induced by phenylephrine infusion. Windkessel model simulation suggested that oscillations in brain blood flow are modulated not only by dynamic autoregulation, but also by changes in steady-state cerebrovascular resistance and/or vascular compliance.

Clockwise, from top left: Rong Zhang, Shayla Derousseau and Benjamin Levine.

The brain has a high metabolic rate, and brain perfusion is vital for neuronal function and survival. Under resting conditions, the human brain receives about ~15–20% of the cardiac output. This demand for blood supply is so imperative that only a few seconds of ischaemia is sufficient to derange brain function profoundly and can result in syncope. Based on the Fick principle, Kety and Schmidt measured brain blood flow for the first time in humans over 50 years ago by using a diffusible inert gas (N_2O) method (Kety & Schmidt, 1945). With the classic Kety–Schimdt method, only whole brain perfusion can be measured and it takes about 10 min to complete one measurement. Over the years, the technology for measuring brain blood flow has been improved substantially. At present, regional brain blood flow can be measured with a spatial resolution of several millimeters and a temporal resolution of about 1 min by using positron emission tomography (PET) or magnetic resonance imaging (MRI).

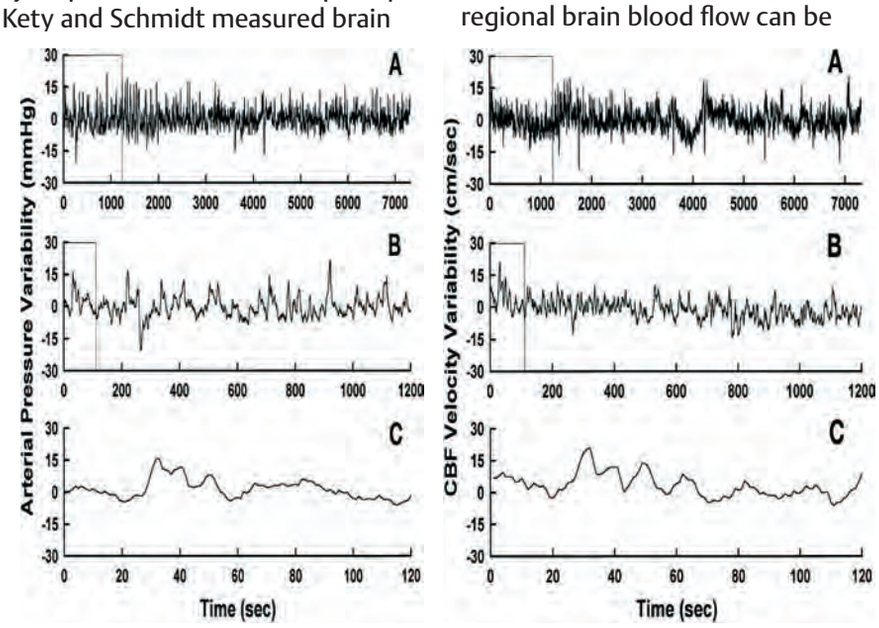

Figure 1. Representative beat-to-beat oscillations in arterial pressure (left panels) and cerebral blood flow (CBF) velocity from one subject (right panels). The upper panels are 2 h of recordings. The middle and lower panels represent the zoomed out periods of 20 min and 2 min of recordings within the marked rectangular boxes, respectively. The steady-state mean arterial pressure and CBF velocity (normalized to be zero for these plots) are 76 mmHg and 67 cm s^{-1} in this subject. Modified from Zhang *et al*. 2000.

Measuring brain perfusion with high spatial and temporal resolution is important because brain perfusion is heterogeneous and dynamic. In this regard, the development of transcranial Doppler (TCD) in the early 80's has provided a powerful tool for measuring dynamic changes in brain blood flow in the basal cerebral arteries with a high temporal resolution of about 10 ms (Aaslid *et al.* 1982). Using TCD, pulsatile changes in brain blood flow in response to pulsatile changes in arterial pressure can be recorded continuously on a beat-to-beat basis. Our earlier work demonstrated that mean cerebral blood flow (CBF) velocity averaged within each cardiac cycle fluctuates spontaneously with various amplitudes over many time scales. In addition, these beat-to-beat fluctuations in CBF velocity are similar to the observed changes in arterial pressure (Fig. 1) (Zhang *et al.* 2000). Assuming that the diameter of basal cerebral arteries (conduit arteries) remains constant, changes in CBF velocity represent beat-to-beat changes in brain blood flow. Notably, the magnitude of spontaneous oscillations in CBF velocity can be as large as 30% of its mean value even under resting conditions, which highlights the dynamic nature of brain perfusion (Fig. 1) (Zhang *et al.* 2000).

However, these observations appear to be at odds with the prevailing concept of cerebral autoregulation which states that brain blood flow remains relatively constant in spite of large changes in arterial pressure. This paradox between the traditional

concept of cerebral autoregulation and the observed large oscillations in CBF velocity may be explained by the limitations of previous studies for measuring CBF. With poor temporal resolution, CBF responses to dynamic changes in arterial pressure could not be revealed.

The following questions then need to be answered: how should the dynamic pressure–flow relationship of the cerebral circulation be quantified, and what are the underlying mechanisms for controlling brain blood flow in response to dynamic changes in arterial pressure. To address these questions, we have demonstrated that the relationship between beat-to-beat changes in arterial pressure and CBF velocity can be quantified by using the transfer function method based on Fourier spectral analysis (Zhang *et al.* 1998). Briefly, we use this method to quantify how each of the frequency components of changes in arterial pressure is transmitted into changes in CBF velocity. Estimation of the transfer function showed that at the frequency range of 0.02 to 0.5 Hz, the dynamic pressure–flow relationship of the cerebral circulation can be described as a 'high-pass' filter. That is, transfer function gain is low at low frequencies and increases gradually with increases in frequency associated with a decline in phase (Fig. 2). These data have been interpreted to indicate that the ability of cerebrovascular beds to attenuate transient changes in CBF in response to changes in arterial pressure is more or less effective depending on the frequency of changes in pressure – a concept which has been referred to as dynamic cerebral autoregulation (Zhang *et al.* 1998).

In this study, to better understand the physiological mechanisms underlying the dynamic pressure–flow relationship of cerebral circulation, we studied the effects of acute cerebral vasoconstriction on the transfer function between changes in arterial pressure and CBF velocity in healthy young to middle-aged subjects (Zhang *et al.* 2009). CBF velocity was measured in the middle cerebral artery using TCD. Arterial pressure was measured either with arterial catheterization or non-invasively using Finapres. Cerebral vasoconstriction was induced by acute increases in arterial pressure with incremental venous infusion of phenylephrine. Phenylephrine is an α1-adrenoreceptor agonist, but does not have direct effects on the cerebral blood vessels since it does not pass the blood–brain barrier. Thus, cerebral vasoconstriction during phenylephrine infusion reflects mainly a vascular myogenic response to acute increases in arterial pressure.

We found that with stepwise increases in phenylephrine from 0.5 to 1.0 and 2.0 μg kg^{-1} min^{-1}, mean arterial pressure averaged over a time period of 6 min increased by 11, 23 and 37%, respectively, from its baseline value of about 83 mmHg under steady-state conditions. However, CBFV increased (11%) only with the highest increase in arterial pressure. Cerebrovascular resistance index, calculated as mean arterial pressure divided by mean CBF velocity, increased progressively by 6, 17 and 23%, demonstrating effective steady-state cerebral autoregulation.

Interestingly, corresponding to cerebral vasoconstriction, transfer function gain at the low frequencies (LF, 0.07–0.20 Hz) was reduced by

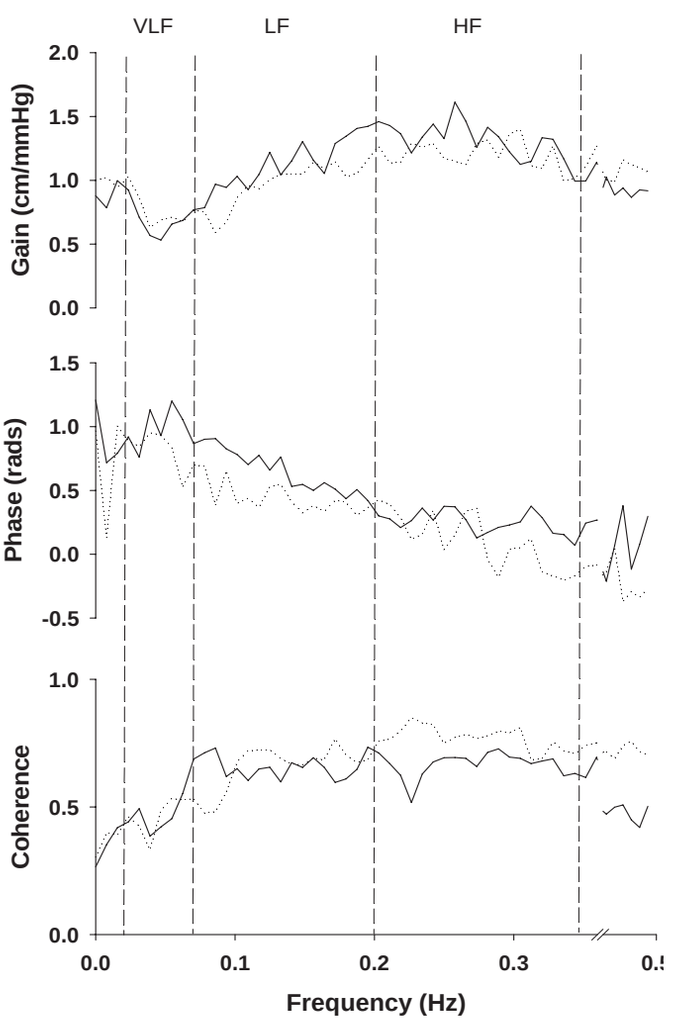

Figure 2. Group averaged transfer function gain, phase and coherence function at baseline (continuous lines) and during phenylephrine infusion at 2 μg kg^{-1} min^{-1} (dotted lines) (n = 13). Dashed lines indicate the very low (VLF), low (LF) and high frequency ranges (HF). Similar changes were observed during 0.5 and 1.0 μg kg^{-1} min^{-1} infusion (for simplicity, these data are not shown). From Zhang *et al*. 2009.

15, 14 and 14%, while the phase was reduced by 10, 17 and 31%. A similar trend of changes was observed at the high frequencies (HF, 0.20–0.35 Hz), but gain and phase remained unchanged at the very low frequencies (VLF, 0.02–0.07 Hz) (Fig. 2).

We speculate that besides dynamic autoregulation, oscillations in brain blood flow in response to changes in arterial pressure also may be influenced by the steady-state increases in cerebrovascular resistance and/or vascular compliance during cerebral vasoconstriction. A three-element Windkessel model was used to test this hypothesis. The model parameters consist of central and peripheral cerebrovascular resistance and a vascular compliance component. These parameters were derived from the experimentally estimated cerebrovascular resistance index and the phase at baseline and during phenylephrine infusion. Windkessel model simulation indicates that increases in steady-state cerebrovascular resistance and/or decreases in cerebrovascular compliance (represented by the model parameter C_P) can lead to reductions in transfer gain and phase (Fig. 3). Notably, the bimodal feature of changes in phase suggests that either decreases or increases in vascular compliance can lead to a reduction in phase depending on its baseline values (Fig 3).

Collectively, findings from this study suggest that changes in steady-state cerebrovascular resistance and/or vascular compliance modulate the dynamic pressure–flow relationship of the cerebral circulation at the low and high frequencies, while dynamic autoregulation is likely to be effective at the very low frequencies. Thus, spontaneous oscillations in CBF velocity, and presumably brain blood flow, are determined not only by dynamic autoregulation, but also by changes in steady-state cerebrovascular resistance and/or vascular compliance.

Spontaneous oscillations in brain blood flow or tissue oxygenation have been observed by using other brain imaging modalities such as functional MRI. There is a great interest in linking these haemodynamic changes with spontaneous brain neuronal activities to study 'functional connectivity'. In addition, transfer function analysis of spontaneous changes in arterial pressure and CBF velocity has been used to assess dynamic cerebral autoregulation in patients with stroke, hypertension and other cerebrovascular diseases. The present study reveals the complexity of the underlying mechanisms for regulating spontaneous oscillations in brain blood flow in response to dynamic changes in arterial pressure which may provide useful information for future studies of brain perfusion in humans.

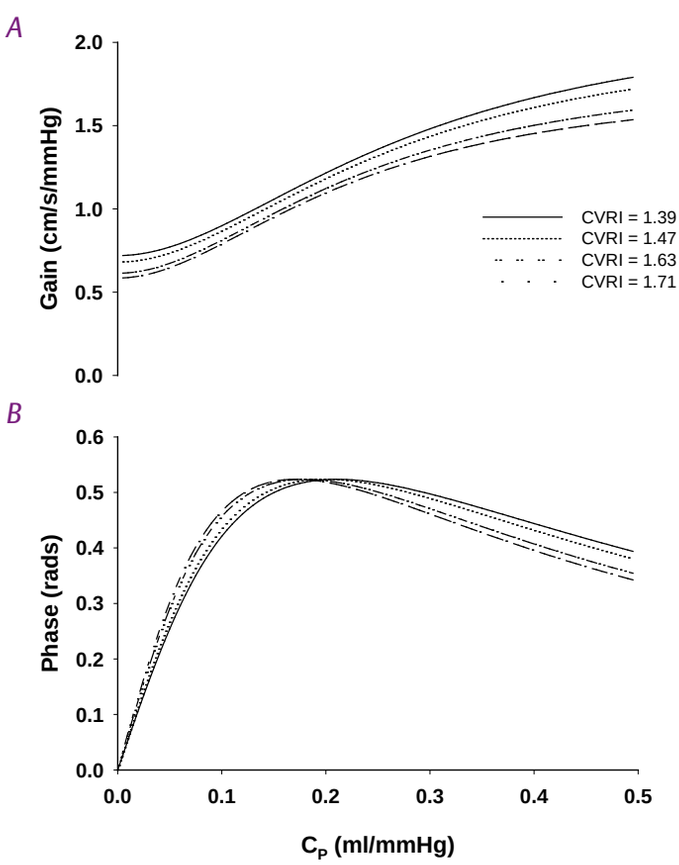

Figure 3. Windkessel model simulation of the effects of changes in steady-state cerebrovascular resistance index (CVRI) and/or vascular compliance (C_P) on the transfer function gain (*A*) and phase (*B*). Increases in CVRI and decreases in C_P during cerebral vasoconstriction can lead to reductions in transfer function gain. Note the bimodal feature of the phase with changes in CVRI and C_P. From Zhang *et al*. 2009.

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Hepatic insulin resistance is induced by high-fat overfeeding in healthy men

Diets high in fat and calories are associated with increased risk of obesity and type 2 diabetes; however, the contribution of metabolic defects to the development type 2 diabetes is controversial

Recent findings have shown that high-fat overfeeding for 5 days results in insulin resistance of the liver but not of the muscle tissue and in increased insulin secretion. Since increased insulin secretion precedes the development of muscle insulin resistance after overfeeding, it is suggestive of a role for insulin in the development of muscle insulin resistance and obesity. Taken together, this underscores the significant adverse effects of fat overfeeding in healthy humans, even during short-term exposures equivalent to commonly occurring feast periods in most societies.

High-fat diet and development of type 2 diabetes

High-fat calorie-rich diets along with physical inactivity have made type 2 diabetes a worldwide epidemic. Although many metabolically active organs may be involved, the development of type 2 diabetes is characterized by three major defects – insulin resistance of the muscle tissue, elevated hepatic glucose production and impaired insulin secretion. However, the relative contribution of muscle and hepatic insulin resistance *versus* defective insulin secretion on development of hyperglycaemia is controversial, and may depend on the dominant underlying aetiology of this multi-factorial disease.

Altered lipid metabolism plays an important role in the pathogenesis of insulin resistance. Accumulation of excess fat as intramyocellular lipid (IMCL) in muscle tissue has been reported to be associated with reduced insulin sensitivity, and it has been shown that mitochondrial function and expression of genes involved in oxidative phosphorylation (OXPHOS) including their key co-transcriptional factor peroxisome proliferator-activated receptor-γ coactivator-1α (*PGC-1α*) are commonly decreased in elderly and obese insulin-resistant and type 2 diabetic subjects (Patti *et al.* 2003; Petersen *et al.* 2004). Dysregulation of intramyocellular lipid (IMCL) metabolism in insulin resistance and type 2 diabetes may be linked with defective OXPHOS, and both short- and long-term fat exposure may play a key role in the development of impaired mitochondrial OXPHOS.

Previous studies have used less-physiological fat exposure experiments using intravenous lipid infusions to induce supraphysiological high levels of plasma free fatty acids (FFA) as a model to study the metabolic effects of high fat exposure, and thereby to mimic the state of overt type 2 diabetes commonly characterized by elevated FFA levels. Other studies have used varying duration of either different types of overfeeding or diets containing high amounts of fat. These studies have mainly included rodents, obese human subjects and/or human subjects with a family history of diabetes, using relatively small numbers. However, the literature is relatively limited with regards to studies of the acute effects of a physiological diet high in both fat and calories on metabolic mechanisms relevant to the pathophysiology of type 2 diabetes in healthy subjects.

Impact of short-term high-fat overfeeding on hepatic *versus* muscle insulin resistance

We recently reported that intake of a high-fat diet (60%) with 50% extra calories for 5 days in healthy young men resulted in an approximately 25% increase of fasting hepatic glucose production (Fig. 1*A*), in spite of an elevated fasting insulin level (Brøns *et al.* 2009). As a consequence of the increased hepatic glucose production, fasting

Charlotte Brøns.

glucose levels were increased by 0.5 mmol l^{-1} after overfeeding, and although within the normal range, elevated fasting glucose does in itself constitute an independent risk factor for developing type 2 diabetes. The fact that only 5 days of high-fat overfeeding increases fasting glucose levels due to hepatic insulin resistance underscores the significant deleterious effects of fat overfeeding *per se* in healthy humans even during short-term exposures, equivalent to commonly occurring feast periods in most societies. When calculating the hepatic insulin resistance index, the finding of an elevated hepatic glucose production after overfeeding was shown to be due to hepatic insulin resistance (Fig. 1*B*). In addition, overfeeding resulted in a significant increase of the liver enzyme aspartate aminotransferase (ASAT), an indication of a stressed liver accumulating fat. Indeed, hepatic steatosis in human subjects is increasingly recognized as a key feature in the metabolic syndrome associated with development of hepatic insulin resistance.

Despite the observed hepatic insulin resistance, whole-body peripheral (muscle) insulin-stimulated glucose uptake was not decreased after fat overfeeding (Fig. 1*C*). Previous studies of short-term fructose and carbohydrate overfeeding did not have an effect on whole-body insulin sensitivity in lean healthy subjects either, and the finding of hepatic insulin resistance without

the presence of muscle insulin resistance after only 5 days of fat overfeeding has not been shown in healthy subjects before. Despite normal whole-body glucose uptake, the insulin-stimulated glycolysis was decreased by approximately 25% by overfeeding, consistent with reports of decreased insulin-stimulated glycolysis preceding overt peripheral insulin resistance during intravenous lipid infusion. However, *in vivo* mitochondrial function was not affected by high-fat overfeeding when measured by ^{31}P-magnetic resonance spectroscopy before and after energy-depleting exercise in two different muscle groups. Furthermore, no differences in basal or insulin-stimulated expression of *PGC-1α* and OXPHOS genes in muscle tissue were observed either. The data therefore do not support the current hypothesis that a short-term high-fat diet reduces the expression of nuclear genes encoding mitochondrial transcription factors involved in mitochondrial biogenesis in healthy young men (Sparks *et al.* 2005).

Assessment of β-cell function in relation to insulin action

Acute intravenous lipid exposure and FFA elevation increases insulin secretion whereas chronic elevation of FFA may cause β-cell dysfunction as a consequence of lipotoxicity. The first-phase insulin response to an intravenous glucose bolus is a sensitive measure of β-cell function. However, assessment of relative β-cell function in humans is challenging because of the complex interplay between insulin secretion, insulin sensitivity and hepatic insulin extraction (Cobelli *et al.* 2007).

In individuals with normal glucose tolerance, an approximate hyperbolic relation exists between β-cell function and insulin sensitivity, where a reduction in insulin sensitivity is accompanied by a compensatory upregulation of insulin secretion (Fig. 2). This relationship between insulin sensitivity and insulin secretion, commonly known as the disposition index, is determined as the product of the two variables, and is thought to be constant for individuals with the same degree of glucose tolerance. Although the conventional view is that increased insulin secretion is a secondary and compensatory response to insulin resistance (Bergman *et al.* 2002), data suggest that the inverse scenario with increased insulin secretion preceding and possibly causing insulin resistance may characterize some metabolic states (Le Stunff & Bougnères, 1994). Interestingly, partly due to insufficient knowledge about the molecular feedback mechanisms and signals between β-cell and insulin action mediating the inverse relationship between the two, the extent to which hepatic or muscle insulin action should be used in the calculation of the disposition index, an issue clearly relevant to data showing discordant results of high-fat overfeeding on hepatic *versus* muscle insulin action, has not even been debated.

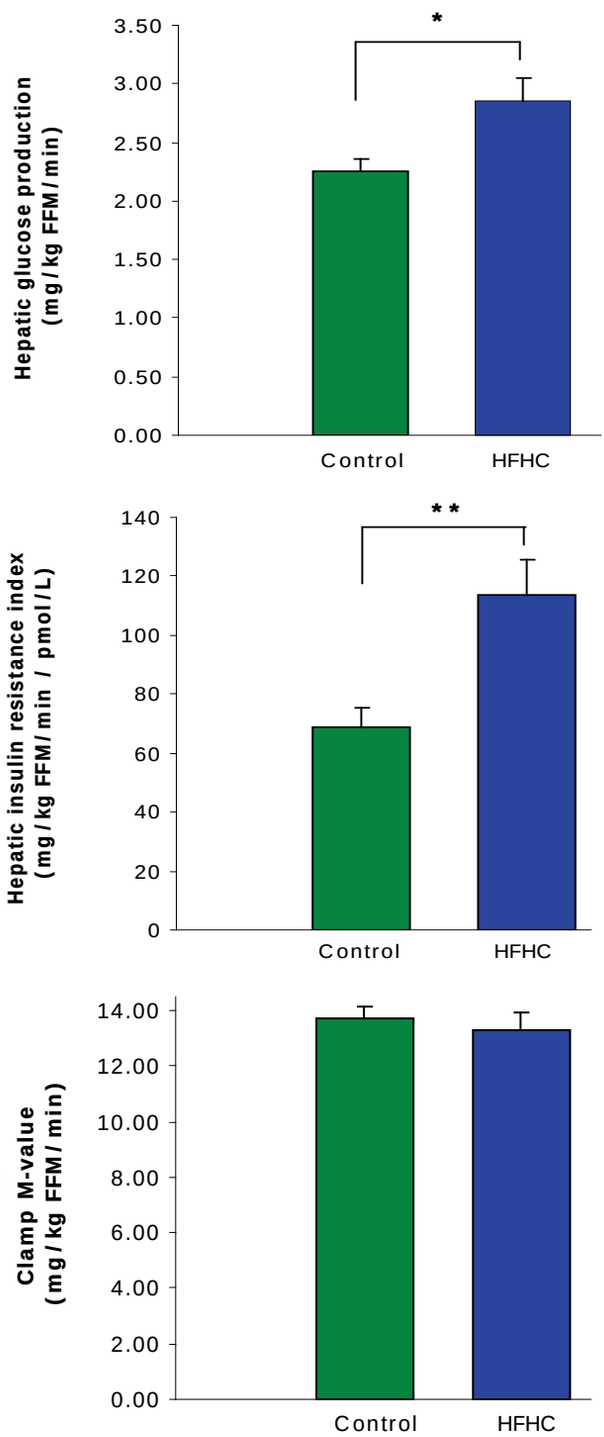

Figure 1. The hepatic glucose production in the basal state is shown in *A*, and the calculated hepatic insulin resistance index in the basal state is shown in *B*. *C* shows the insulin-stimulated glucose disposal i.e. the clamp M-value. Control diet (green) and high-fat high-calorie (HFHC) diet (blue). FFM, fat-free mass. Data are mean ± S.E.M. $^{*}P \leq 0.05$, $^{**}P \leq 0.005$ (Brøns *et al.* 2009).

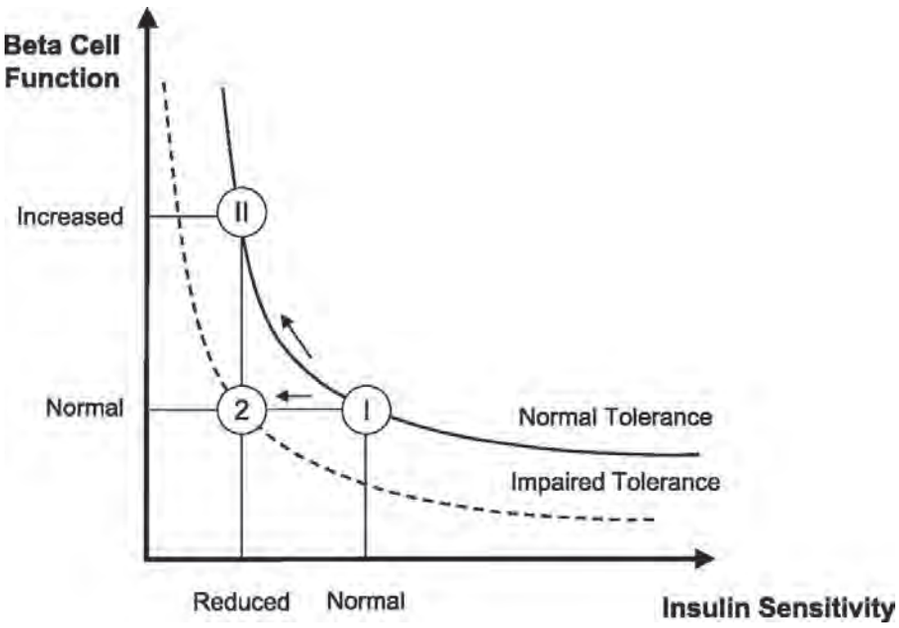

Figure 2. The importance of expressing the β-cell response in relation to insulin sensitivity is illustrated by using the disposition index, that is the product of insulin secretion and insulin sensitivity which is assumed to be a constant. With deviation from this hyperbola, deterioration of glucose tolerance and type 2 diabetes occurs. (Modified from Cobelli *et al.* 2007.)

We showed that high-fat overfeeding resulted in significantly elevated insulin secretion, and the disposition index was subsequently calculated in two ways: either hepatic or muscle insulin action. When including muscle insulin action in the calculation, a disproportionately elevated insulin secretion in relation to muscle insulin action was observed. However, when including hepatic insulin action, the disposition index was unaltered by high-fat feeding, indicating appropriate compensation of the β-cell. This indicates that the increased insulin secretion could possibly compensate for the hepatic insulin resistance and precede the development of muscle insulin resistance in young men, thereby suggesting that hyperinsulinaemia may be causally related to the development of muscle insulin resistance and obesity after longer periods of high-fat feeding. However, we are not able to determine the extent to which increased insulin secretion may precede the development of hepatic insulin resistance. Taken together, the data therefore indicate that the adjustment for hepatic insulin sensitivity in the calculation of the disposition index provides different information to that of peripheral insulin sensitivity, and helps to improve our understanding of the complexity of *in vivo* estimation of β-cell function in relation to insulin action.

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Reminiscences of Bayliss and Starling

Exam technique

In 1963 Charles Lovatt Evans gave the first Bayliss–Starling Lecture. This lecture was established by The Physiological Society in memory of W. M. Bayliss (1860–1924) and E. H. Starling (1866–1927). He had many anecdotes, particularly about Bayliss who, as a medical student, failed his anatomy. In his oral the examiner said 'Your written answer to that question on the cords of the brachial plexus was extraordinary – wherever did you get it from?' to which Bayliss replied, 'Well, I never could memorize that sort of thing so I put it the way I thought it should be'.

Priorities

Lovatt Evans commented on Bayliss's gentle nature and unworldiness. He said that when Bayliss was instructed to go to Buckingham Palace to be knighted he replied that as the date coincided with that of a meeting of The Physiological Society, he would be unable to attend.

British sportsmen

Both Bayliss and Starling played tennis. At the IUPS Congress in 1926 Starling said the reason why the British excelled in science was because they were devoted to sports, and research was the greatest sport of all. In response the French physiologist and endocrinologist Gley, claimed France as the berceau (cradle) of physiology.

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Is the motor system at rest while we are sleeping?

A commonly held belief is that the motor system is at rest in sleep, because we barely move – and if we do move it is often pathological. But this assumption might not be entirely true. There is evidence that elements of the motor system remain functionally coupled in sleep in ways specific for each sleep stage, perhaps to allow physiological movements in sleep and to facilitate motor learning

With the advent of more refined methods to study the physiology of sleep it gradually became evident that sleep is associated with highly dynamic changes in cerebral activity. A variety of different brain rhythms (i.e. oscillations) have been extensively described in simultaneous recordings from cortical and thalamic neurons in naturally sleeping animals (Steriade, 2006). These rhythms orchestrate the cyclic occurrence of non-rapid eye movement sleep (including slow-wave sleep) and rapid eye movement (REM) sleep across a night. At sleep onset three cardinal rhythms – sleep spindles (12–17 Hz), delta (1–4 Hz) and slow oscillations (0.5–1 Hz) – are generated in cortico-thalamic networks. As a common feature, all these rhythms are associated with prolonged hyperpolarisation of thalamocortical and neocortical neurons which inhibit the cortico-petal transmission of sensory signals, and thus allow the cortex to disconnect from the rest of the brain and the individual to effectively fall asleep (Steriade, 2006). In humans, the same oscillations have been identified to be highly coherent across different cortical sites during non-REM stage 2 (N2) and slow wave sleep (N3) (but not in REM), as revealed by frequency analysis of the scalp electroencephalogram (EEG) (Achermann & Borbély, 1998). In fact, the spontaneous generation of these rhythms has challenged the previously held assumption that neuronal networks are 'inactive' during sleep. Current investigations now address the question of whether these rhythms play a functional role for learning and cognition apart from just initiating and maintaining sleep.

Farid Salih (left) and Pascal Grosse.

In our recent study we asked how these sleep-specific brain rhythms translate into the functional organisation of the motor system (Salih *et al*. 2009). As a change of perspective we were thus looking into the physiology of a

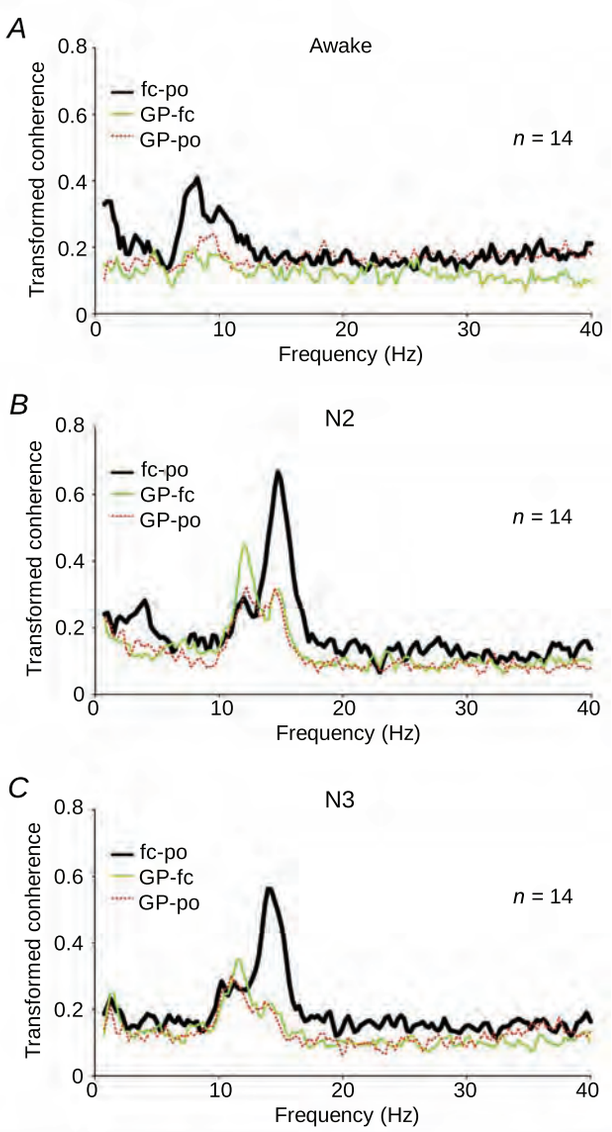

Figure 1. Group averaged transformed coherence spectra between recording sites in the three states of vigilance. In wakefulness (*A*) the coherence spectrum for surface EEG (fc-po) shows a broad-based peak between 7–12 Hz. For the combinations between GP and the two cortical sites the same peaks are present, though they are much smaller. In N2 (*B*), coherence between both cortical sites shows a prominent 13–17 Hz peak, preceded by a peak at 10–12 Hz. Between GP and the fronto-central cortex the 10–12 Hz peak exceeds that seen between both cortical sites and is also more pronounced than the 13–17 Hz peak. Both coherence peaks are also present between GP and parieto-occipital cortex. In N3 (*C*), the same 13–17 Hz peak is present in the coherence between both cortical sites; however, the peak frequency is slightly lower than in N2. The 10–12 Hz peak remains present. In coherences between GP and the two cortical areas, the 13–17 Hz peak is almost indiscernible while the 10–12 Hz peak persists.

circumscribed functional network. A novel approach to study a functional neuronal network in human sleep is to record surface EEG along with local field potentials from depth electrodes in patients who undergo deep brain stimulation (DBS). While the electrodes are externalised it is possible to record signals from the DBS target areas. For our investigation, we studied seven patients undergoing DBS of the globus pallidus (GP), a motor element in the basal ganglia loop, to treat dystonia. With simultaneous recordings of local field potentials from globus pallidus and regular scalp EEG in N2, N3, REM and wakefulness, we used a set of methods pertaining to frequency analysis to look into the functional coupling between globus pallidus, motor and visual cortex. Frequency analysis investigates neuronal oscillations and is based on the cross-correlation between two separate signals in the time and frequency domain (Grosse *et al*. 2002). The most important measures applied in our study were coherence and the directed transfer function (DTF). Coherence is the principal measure of the linear dependence or

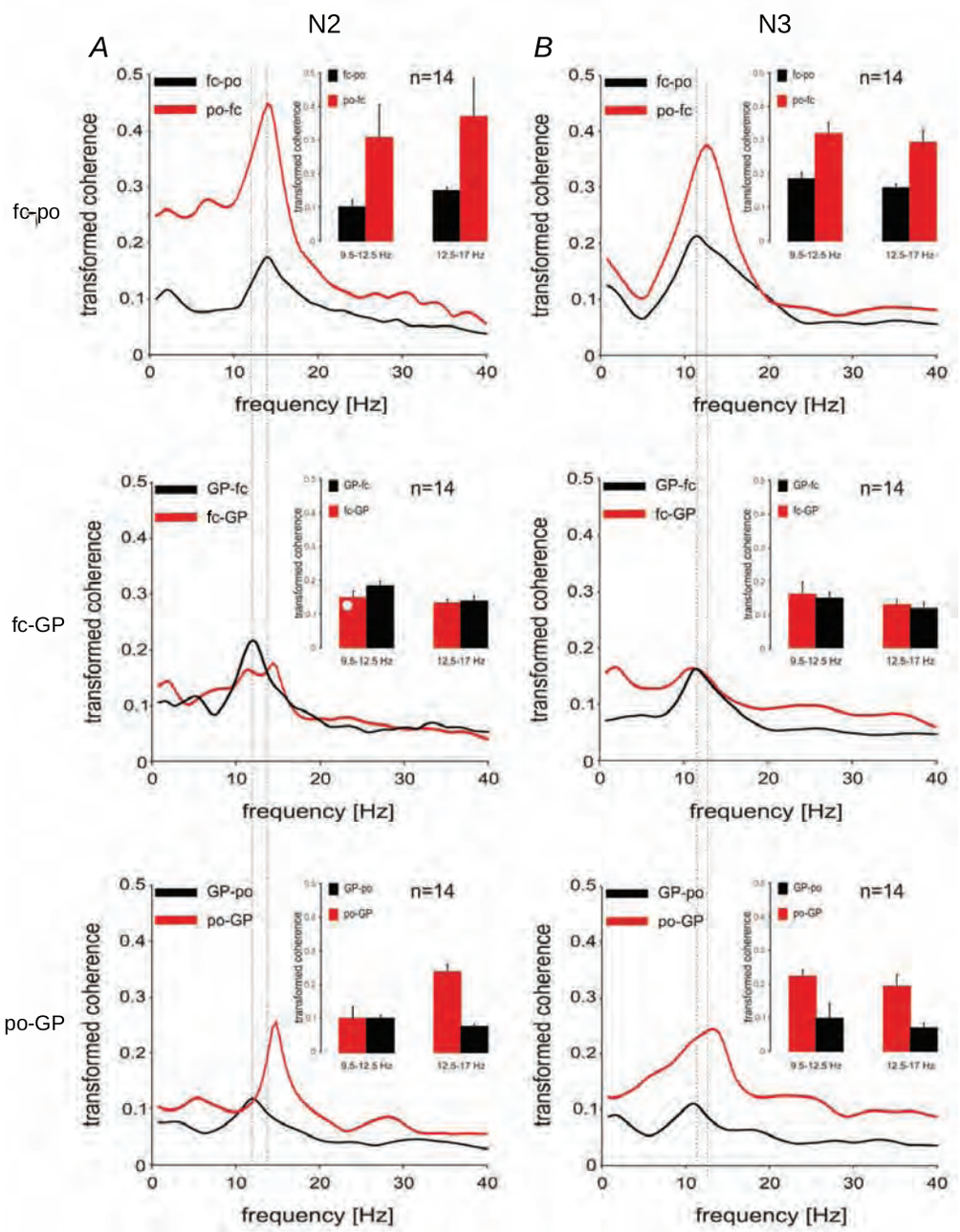

Figure 2. Pooled results for DTF (directed transfer function) for N2 and N3 for the various combinations of the three recorded sites. Lines indicate directed (transformed) coherence spectra, insets averaged coherences for the frequency bands of 9.5–12.5 and 12.5–17.0 Hz (± S.E.M.), respectively. Each figure represents the directed coherence from one site to another and that in the opposite direction. Peak frequencies from GP to other sites are always in the range of 9.5 to 12.5 Hz. Flows from parieto-occipital cortex always peak in the higher frequency band for sleep spindles (13–17 Hz). The peak at 9.5–12.5 Hz linked to GP becomes most prominent when the DTF from GP to fronto-central cortex is considered in N2. Coherences are much higher in drives from parieto-occipital cortex to all other sites.

correlation between two signals in the frequency domain. It is mathematically bounded between zero and one, where one indicates a perfect linear relationship and zero indicates that the two signals are not linearly related at a particular frequency. The DTF investigates any possible asymmetry in the flow of coherent activity between signals (Kaminski & Blinowska, 1991). Where the DTF of coherent activity at two recording sites is asymmetric, the 'effective direction of coupling' predominates in one direction. However, neither coherence nor an asymmetrical DTF necessarily implies a direct connection between the two areas in which activity is recorded. Thus, information can be transferred indirectly between recorded structures, via one or more unrecorded structures, or activity in both recorded structures may be driven by a third unrecorded structure.

In our study, we could identify significant coherence between globus pallidus and motor cortex as well as between globus pallidus and visual cortex in frequency bands specific for sleep (i.e. 9.5–17 Hz in both N2 and N3, 0.5–4 Hz in N3, Fig. 1*A*–*C*). Importantly, there appear to be two different physiological activities represented within the broad band of significant coherence from 9.5 to 17 Hz in non-REM sleep. As expected, there was a component in the range of sleep spindles with a maximum centred at ~14 Hz. This was best seen in the coherence between motor and visual cortex as well as between globus pallidus and both cortical sites during N2, and between motor and visual cortex in N3. The DTF suggested that the spindle frequency component was preferentially driven from visual cortex (Fig. 2*A*–*C*). The second component consists of an activity in the α-band (9.5–12.5 Hz). This coherent α-rhythm was elevated especially between both components of the motor system, i.e. globus pallidus and motor cortex. The DTF further suggested that this α-rhythm consisted of a preferential drive from globus pallidus to the motor cortex in N2 and a more symmetric drive in N3.

Based on the extensive evidence from intracellular thalamo-cortical recordings in naturally sleeping animals, the coherence patterns we identified between globus pallidus, motor and visual cortex in the range of sleep spindles are most probably explained by a common 'third' generator, namely the reticular thalamic network. In contrast, our results for coherence in the α-band are consistent with more direct functional coupling between globus pallidus and the motor cortex in non-REM sleep. It has long been established that α-rhythms can be a feature of non-REM sleep in surface EEG, particularly during slow-wave sleep. However, until recently the significance of this α-rhythm had been unclear. Our data now link the α-rhythm more specifically to the motor system as its potentially specific signature. Focussing on δ-waves and spindle rhythms, other studies have recently associated these oscillations to brain networks involved in memory consolidation (Huber, 2004). Functionally, procedural memory formation may require slow-wave sleep rhythms, and also training on a declarative task increases sleep spindle density significantly (Gais *et al*. 2002). From a physiological point of view, the strong coupling between motor cortex and the basal ganglia in the α-frequency band might indicate, by analogy, the reshaping of synaptic plasticity in motor circuits and the levelling of the amount of movements while motoneuron activity is largely reduced during sleep. With a clinical perspective in mind, it is also tempting to hypothesise that modifications of this α-rhythm are somehow involved in the generation of the many sleep-related movement disorders.

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High-resolution displays for high-resolution data

In order to effectively explore the high-resolution datasets being produced by advanced non-invasive organ scanning technologies, it is imperative to use new methods of visualisation. We describe how we have used a tiled wall of multiple LCDs to analyse large biomedical images, from histological sections to three-dimensional (3D) MRI tissue volumes

Advances in the technology used for scanning biological samples means that data are being collected at far larger magnification than thought possible, in particular using non-invasive techniques. While providing unprecedented detail, they consist of much larger datasets than have previously been considered. This poses challenges for both the visualisation and analysis.

We describe a collaborative project between the Departments of Physiology, Anatomy and Genetics, the Computing Laboratory, and Cardiovascular Medicine at the University of Oxford, and the School of Computing at the University of Leeds, to develop techniques for high-resolution visualisation of both 2-dimensional (2D) and 3-dimensional (3D) cardiac structure data. As an exemplar application, we are considering an individual rabbit heart which has been scanned by the group of Jürgen Schneider non-invasively, using high-resolution (11.7 T) MRI giving 25 µm voxel resolution. This heart was then serially sectioned to provide histological images with in-plane pixel dimensions of 0.546 µm x 0.546 µm. The quantity of data from these sets is approximately 1.5 GB for the MRI data, and 1.4 TB for the histology stack (see Burton *et al.* 2006; Plank *et al.* 2009).

Visual exploration of high-resolution datasets such as these is normally limited by the available display 'real estate'. The numbers of pixels on a standard computer screen is typically between 1 and 2 megapixels. In contrast, each 2D slice typically consists of up to 32 000 x 32 000 pixels, i.e. more than a gigapixel. The MRI volume for the rabbit heart consisted of 1440 slices with 1024 x 1024 in-plane pixels, i.e. forming about a giga-voxel. Being able to expand the available screen size is therefore very important. However, such expansion must be designed with usability for the end-users in mind.

The development of high-resolution display walls, such as shown in Fig. 1, offers a cost-effective way to aid the exploration of extremely high-resolution data. The wall at Leeds (shown) constitutes a total display space of 53.7 megapixels, distributed across 28 LCD panels. Such a display can only be controlled from an interconnected set of computers. The challenge of writing an effective visualisation application to run in parallel on such a computer cluster, and of giving users intuitive and interactive control over the scene, is discussed here. We will illustrate techniques for viewing both 2D and 3D images, but first we address the user control that is common between both applications.

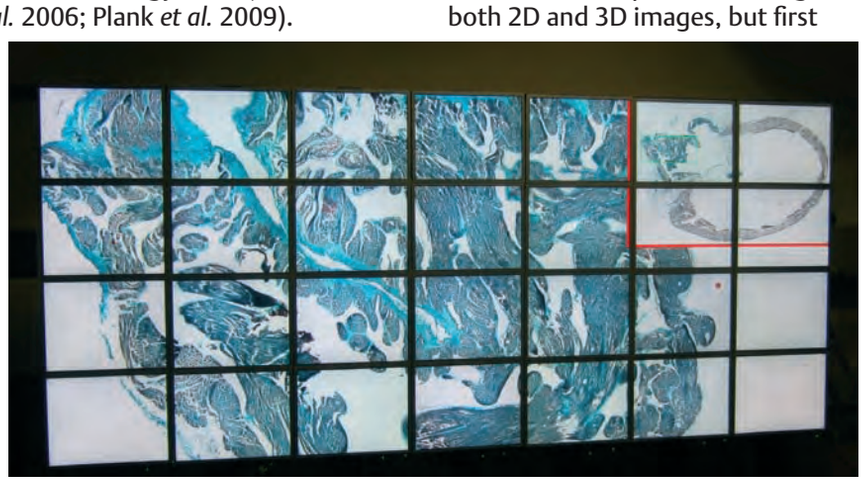

Figure 1. 2D histology image shown on the 53.7 megapixel display wall. The thumbnail view is shown in the top-right corner of the display, whilst the high-resolution part of the image focuses on a tissue region around the aorta.

Clockwise from top left: Christopher Goodyer, John Hodrien and Peter Kohl.

Common features

There are several options available for designing portable parallel visualisation applications that are suitable for tiled displays. We discuss these in Goodyer *et al.* (2009) and explain our choice of VR Juggler (Bierbaum *et al.* 2001), both for 2D and 3D viewers. This has allowed us to develop portable software that may be used at multiple sites, currently including Leeds, Oxford and Baltimore, and that may effectively be scaled to varying needs, from desktop systems to display walls, without recompiling.

For navigation in a high-resolution scene on a display wall, it is important that users are free to combine software and physical navigation, i.e. that they can manipulate the displayed data, and walk around to look at different aspects of the image. Using standard desktop input devices, such as a keyboard or mouse, is therefore not practical. Instead we have found that the use of a wireless 'joypad' (computer games controller) gives even inexperienced users an intuitive interface for navigation.

Navigation functions provided include zooming, panning, rotation and translocation. By controlling

these from the analog controls on the joypad, very fine adjustments of the view are possible. Such changes are not usually possible in 'on-line' situations, such as when using microscopes involving lens changes to alter magnification. By eliminating these discontinuities in the view, it aids exploration and cognition of the biomedical data set.

When exploring high-resolution scenes, it is easy to 'get lost' in the data. For this reason, we provide an additional thumbnail view in one corner of the wall. This enables the user to navigate the image space, viewing two different zoom levels simultaneously.

The program further allows one to attach alpha-numerical labels to relevant features in the loaded files. These are helpful for repeat viewing, collaboration and teaching. In addition, it is possible to store navigation points, so that the user may 'jump' between preset areas of interest. These waypoints can be used to replay sessions and animate presentation between waypoints.

2D viewer

Scanning stage microscopes provide a very powerful tool to image samples with limited user interaction. These microscopes use high-precision stages to translate the sample between microscopic snapshots, which are then 'tiled' together to form a continuous high-resolution image of samples that can be much larger than the actual field of view. The smooth zooming operations described above make it possible to obtain pixel-perfect high-resolution images, displayed at whatever magnification is required by the user (Fig. 1).

The scanned images are stored in a pyramid tiled TIFF format, in which the images have been re-sampled at a range of magnifications below the finest level (at which it was scanned). Thus, only the tiles appropriate to each viewing area need to be loaded into computer memory, while – based on the hierarchy of magnifications available – tiles with the next higher or lower resolution can be pre-loaded, so that the user barely notices the change between resolution level. This approach is similar to those used in popular earth-mapping applications that can be run over the internet.

The image viewer has been developed to load images of any size and render them on either desktop or tiled displays. This work is described in greater detail in Treanor *et al.* (2009) for a related application. The largest image we have tested thus far was 170 000 x 100 000 pixels (or 17 giga-pixels), although there are no architectural limits.

Figure 2. Rabbit whole heart 3D MRI volume, viewed as a long-cut through the left ventricle (apex pointing to the left), with papillary muscles and free-running Purkinje fibres visible, along with labels in the volume (PF, purkinje fibres; PM, papillary muscle, LV, left ventricle; L-AV, left atrio-ventricular valve.

3D viewer

Exploring volumes of data, such as are produced by MRI or CT scans, is becoming increasingly important for clinical diagnoses, as non-invasive imaging modalities are improving in resolution, processing time and affordability. This makes it important to design applications that can exploit perception of 3D structures, as this supports understanding in a way that cannot be obtained by looking at multiple 2D slices of the same volume.

We have constructed a simple isosurfacing operation that produces detailed, but smooth, boundary information from the cardiac MRI data volume described before. We have used freely available open source tools to do this, and have then performed some small transformations in order to improve the performance of the viewer (see Goodyer *et al.* 2009 for details). An additional lower resolution representation of all volume data is used during dynamic changes in display content, to speed up navigation. Once stationary, the high-resolution version of view is shown.

For 3D viewing, additional controls are needed, such as the ability to freely rotate the sample in space. Another addition is the ability to add a 'clipping plane', which can be used to 'section' the data without moving the viewer's position. This enables one to 'strip away' tissue, to reveal structures that otherwise would be hidden from view.

Of course, surface rendering works best when one views tissue from 'the outside'. Once a cutting plane crosses tissue and non-tissue areas (such as cardiac muscle and cavity volume), intuitive realisation of the image can be aided by adding texture to tissue, using the original MRI slices. Further off-line segmentation of relevant features of an organ, for example, the cardiac coronary vasculature, can be overlaid and labelled (Fig. 2).

Conclusion

The increasing availability of very high-resolution/very high-volume

clinical and research visualisation data sets offers immense benefits for basic science and clinical applications – if they can be visually explored in a way that takes advantage of the information content and supports intuitive and dynamic user interaction. The technologies required to do so also provide a remarkable tool for education and training. The tools we described here have been developed with cost, efficacy and transferability in mind. Routines have been built for generic applications, rather than a specific dataset. We hope that they will help to support visual exploration of bio-medical data in a seamless and efficient way and we are very happy to work with new research partners.

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Undergraduate Prize for Physiology 2009

Each year, The Society offers our Society Representatives the opportunity to nominate a student from their institution to receive an Undergraduate Prize for Physiology. Nominations can be for an outstanding student who has performed consistently well throughout their degree or for a student who has completed the best BSc Honours physiology research project.

The successful nominees are listed below:

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Andrew Taylor Grey	Newcastle University
Josephine Collyer	Oxford University
Oisin Quinn	Queens University, Belfast
James Peter Waugh	St George's, University of London
Julie O'Neill	University College Cork
Eric Lucking	University College Dublin
Holly Pattenden	University College London
Jemma Sophie Ransom	University of Aberdeen
Catherine Rowan	University of Bristol
Nicola Platt	University of Cambridge
Samantha Olney	Cardiff University
Christoff du Plessis	University of Dundee
James Hockridge	University of Edinburgh
Andrea Price	University of Huddersfield
Charlotte Binks	University of Leicester
Laura Dearden	University of Liverpool
Sophie Ivil	University of Nottingham
Kai Yoon Fan	University of Sheffield
Kara Marie Panetta	University of St Andrews
Melvina Wanjiru Mungai	University of Strathclyde
Claire McIntyre	University of Sunderland
Cathryn A. Weston	University of Warwick
Yogeshwari Bhadresa	University of Westminster
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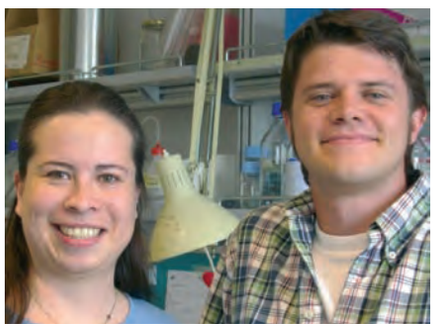
The prize winners are awarded a prize of £100, free Society membership for 1 year and a certificate of achievement. Many additional students were also awarded 'runner-up' prizes of a year's free Society membership.

We offer congratulations to all students.

Is sensory adaptation also regulated by nuclear feedback?

Classically, sensory transduction is believed to take place solely in the cytoplasm of the cell. However, recent evidence suggests that nuclear feedback could contribute to light adaptation

For a long time, it was believed that all processes involved in sensory transduction are delimited to the cytoplasmic compartment. Receiving input such as an odour, touch or a flash of light initiates a cascade of events that codes for a signal that ultimately reaches the brain. In order to maintain efficiency, all these phenomena are fast and the sensory neurons, capable of sensing and converting the signal, must possess a ready-to-use machinery able to reach a high degree of effectiveness. Historically, sensory transduction has been viewed as an event that occurs in less than 1 s and is composed of several faster events; for this reason, scientists have mainly focused their attention on what happens at the periphery of the cell, ignoring potential nuclear involvement. If the nucleus is involved, it will regulate the level of transcription of genes encoding for enzymes and factors, influencing the signal transduction cascade. Of course, considering the time in which a nuclear feedback could happen, it is difficult to think



Clockwise from top left: Diana Bedolla, Paolo Codega and Vincent Torre.

of a role of the nucleus in sensory transduction but adaptation could be affected by nuclear feedback.

Among the different sensory systems, phototransduction is well characterised. The initial example of phototransduction was made by Wilhelm Kuhne in the 19th century, who published in the first issue of *The Journal of Physiology* the identification of rhodopsin, the first G-protein-coupled receptor (GPCR) (Kuhne, 1878). Among the milestones achieved in unraveling the phototransduction mechanisms were the discoveries of the light-dependent hyperpolarisation of the photoreceptor membrane (Tomita, 1970; Baylor & Hodgkin, 1973), the 'dark current' (Hagins *et al*. 1970), the first arrestin protein (Kuhn, 1978; Wilden *et al*. 1986), the identification of the first cyclic nucleotide-gated channel (Fesenko *et al*. 1985) and in 2000, the rhodopsin crystal model, which represented the first crystallographic structure of a GPCR (Palczewski *et al*. 2000). This sophisticated and elegantly organised biochemical pathway nowadays represents one of the best-characterised G-protein-coupled signalling pathways (Fig. 1). Phototransduction starts with the absorption of a photon that, by activating rhodopsin (R^*), leads to the activation of phosphodiesterase

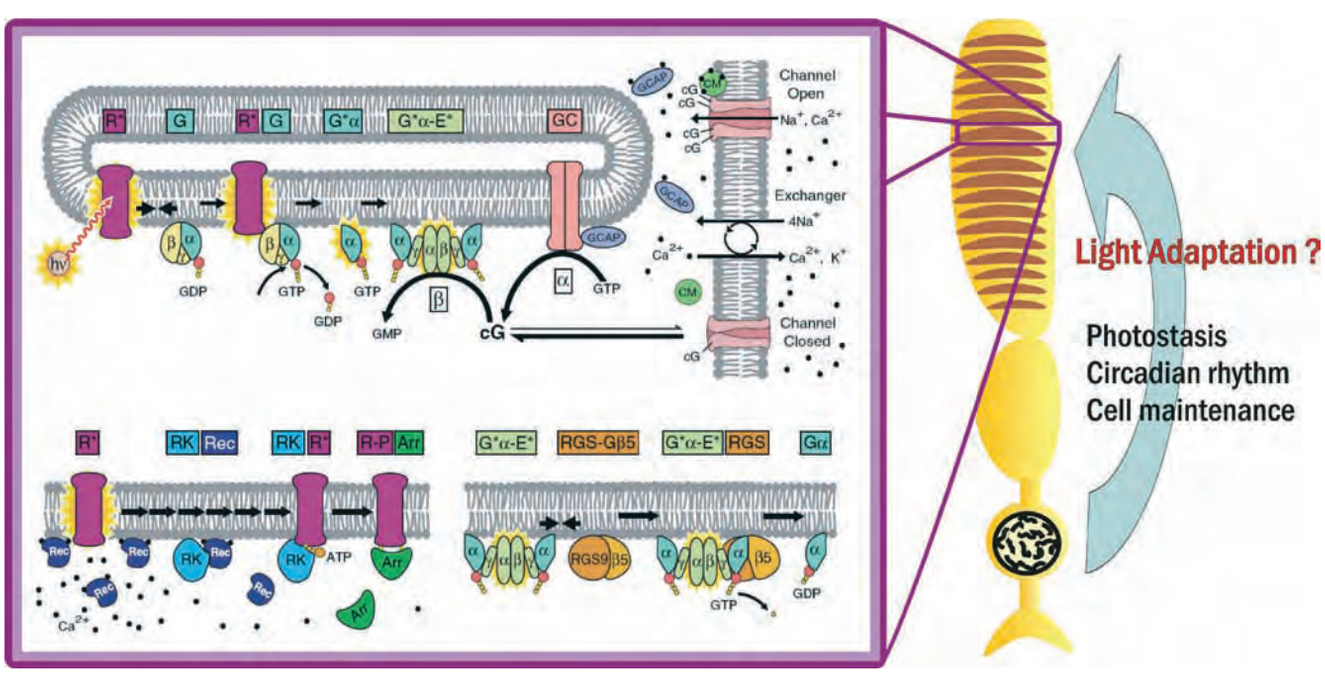


Figure 1. The classical view of phototransduction is limited to events happening in the membrane of the outer segment. In photoreceptors, genomic contributions have been found to influence the circadian rhythm and the photostasis processes; in our work, we investigated whether the nucleus could play its own role also in regulating light-adaptation mechanisms (adapted from Pugh & Lamb, 2000).

(E*), via the G-protein transducin (G*α), causing a drop of the cytoplasmic concentration of cGMP (cG) and, ultimately, the closure of the cyclic nucleotide-gated (CNG) channels. This process is terminated by the binding of arrestin to the phosphorylated rhodopsin (R-P Arr) (Pugh & Lamb, 2000) (Fig. 1). This process takes place in the sensory neurons called photoreceptors with the final physiological outcome corresponding to a hyperpolarisation of the membrane potential caused by the inhibited ion influx (dark current) after closure of the CNG channels. A striking property of photoreceptors is their ability to operate over a vast range of light intensities that span over ten orders of magnitude, a process known as *light adaptation*. There are several mechanisms involved in this phenomenon, and some of them are Ca^{2+} dependent such as those mediated by recoverin, calmodulin and guanlylate cyclase-activating proteins (GCAPs). In general, all of the light-adaptive processes are slower than phototransduction *per se* and therefore, considering the difference in time scale, we hypothesised that the nucleus could come to the scene as an important component in adaptive sensory transduction.

To address this issue, we screened using the DNA microarray technique on isolated light/dark-exposed photoreceptors and then confirmed with real-time PCR the up-regulation of three genes involved in phototransduction: *Sag*, the gene coding for arrestin, and *Guca1a* and *Guca1b*, coding for guanylate cyclase activator protein 1 and 2 (GCAPs), respectively (Codega *et al*. 2009). After 2 h of continuous illumination, we observed that the mRNA transcript level of these genes increases about two-fold for up to 12 h (Fig. 2*A*) and shows intensity-dependent behaviour. After demonstrating that this up-regulation leads to an increase of the content of their related protein, we wondered what was the physiological role of these factors. Arrestin is a potent effector for terminating phototransduction – its binding to the activated rhodopsin stops activation of the phosphodiesterase and leads to an increase of cGMP. On the other hand, GCAPs have an adaptive role: they stimulate guanylate cyclase (GC) in light (when Ca^{2+} level is low) in synthesising cGMP, and they inhibit GC in the dark. Therefore, an increase of arrestin and GCAPs during illumination could lead to an elevation in cytoplasmic cGMP, by increasing the efficiency of phototransduction deactivation and speeding up the GC activity. This could result in the reactivation of the dark current. To investigate

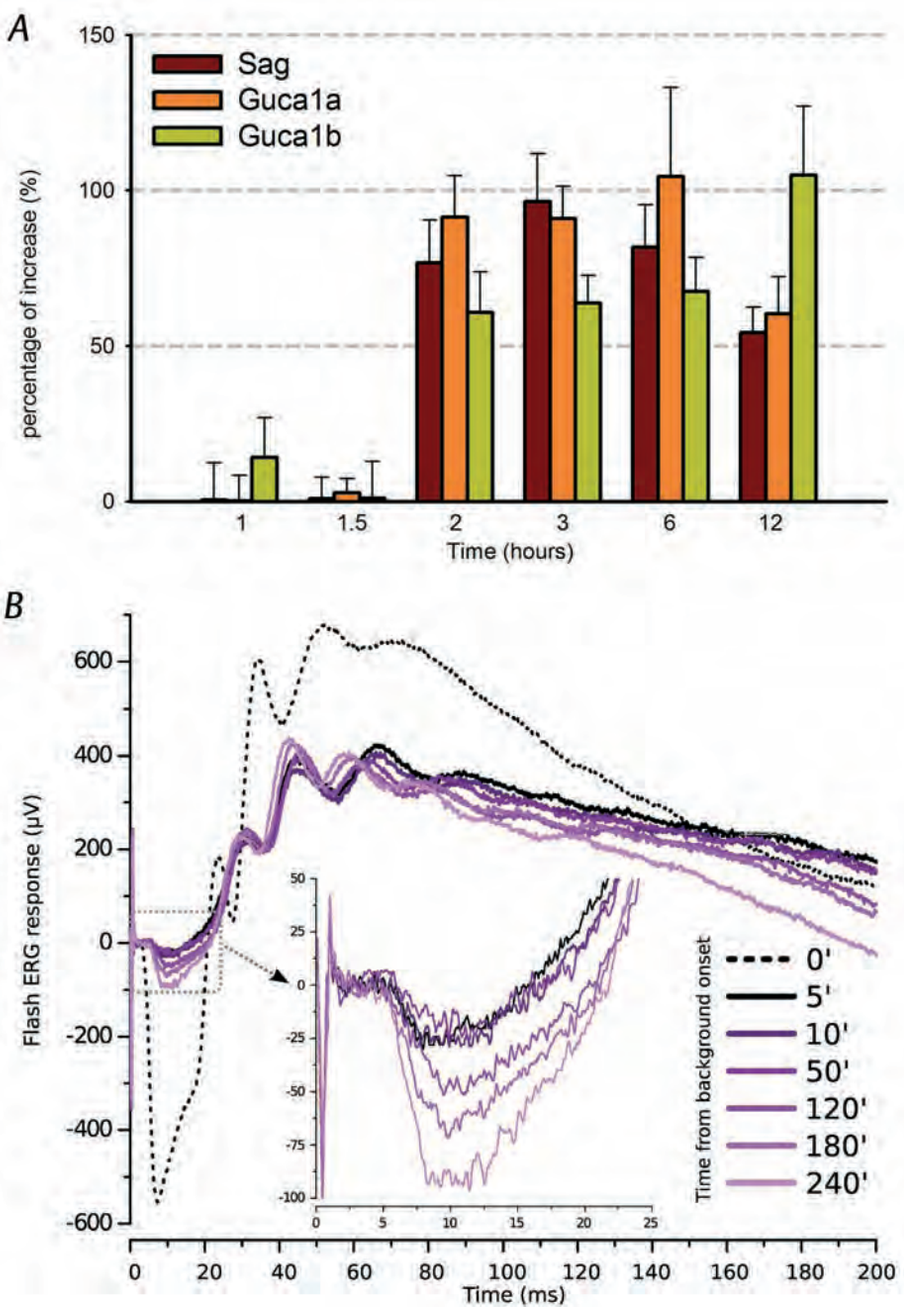


Figure 2. *A*, time course of changes in gene expression (related to the control level in dark conditions) induced by light of *Sag*, *Guca1a* and *Guca1b* in retinas harvested from mice exposed to an ambient light of 1000 lux (mean ± S.E.M.; $n \geq 6$). *B* represents ERG recordings in dark-adapted conditions in response to a bright light flash (dotted curve) and at different times after the onset of a steady light that initially suppressed almost all the photocurrent. The steady light was switched at time 0 and the first recording was obtained 5 min after initiation of the background light (black curve). Responses at later times are shown as shaded purple curves. The inset reproduces the ERG responses in the dotted box.

this, we performed functional *in vivo* electroretinographic tests (ERG) in which the electrical retinal response to a bright light flash is recorded under the same light conditions used for the genomic experiments (Codega *et al*. 2009). The representative recording shown in Fig. 2*B* displays a partial recovery of the a-wave (hyperpolarising wave generated by photoreceptors); the amplitude of the a-wave was more than doubled after 240 min using background light levels that had initially almost completely suppressed the response. Intensity-dependent recoveries were always observed under the different conditions tested. These results indicate the existence of a causal relation between the observed gene up-regulation and the recovery of the photocurrent.

This work strongly suggests that the effect of light in phototransduction is not limited to events occurring in the cytoplasm, but acts also in the nucleus by regulating gene transcription. These findings open up new perspectives in the study of molecular mechanisms in sensory adaptation and, since visual and chemical transduction show great similarities in their signalling cascade, we expect that a genomic component of sensory adaptation may be present also in chemical sensory transduction and possibly also in other sensory receptors. A genomic contribution to sensory adaptation may not be confined to sensory neurons but could be present in the retina and also in the downstream elements of the perception pathways of the central nervous system. We believe that there is a place for a new player in the sensory processing and further efforts should be dedicated to unravel the role of a nuclear feedback in sensory systems.

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Young Physiologists' Bursary Scheme (YPBS)

The YPBS has been created to encourage young physiologists to attend their first Scientific Meeting of The Society. The Scheme is open to undergraduates, postgraduates and recently qualified postdoctoral workers with an interest in physiology, who wish to attend a Society Meeting but do NOT wish to present any work.

Affiliate Members of The Society who wish to present at a Meeting are eligible to apply for travel grant funding of up to £500. If you are not a Member, but would like support to present work at a Meeting, please consider joining.

Funding

The YPBS provides up to £200 to cover the following expenses:

- Meeting registration
- Standard class rail travel, or equivalent
- Conference dinner
- Two nights' accommodation costs in student hostels, or in hotels, guest houses, etc., when their charges are equivalent to those of student hostels

The bursary is available only once for each individual.

Applications

Young physiologists who meet the eligibility criteria outlined above should register in their own right by completing the online Meeting registration form and emailing sbarnsley@physoc.org indicating that they have registered and wish to be considered for a bursary. Please note that bursaries cannot be guaranteed therefore all fees are payable in advance of the Meeting.

Applicants who are not Affiliates of The Society must be sponsored by an existing Member of The Society. Permission from the Member (for sponsorship) must be sought before registering.

For full information, please visit the Society website.

Techniques series

About a year ago, The Physiological Society surveyed affiliates about which techniques they felt should continue to be supported as sponsored workshops and which new techniques they would like to see introduced. Microarray data analysis and bioinformatics was one area that respondents indicated was not currently covered by The Society's educational programme. As a direct response to this, I will be writing or commissioning articles for an educational series on this topic in *Physiology News*, the first of which appears in this issue. If popular, this may be expanded to include other techniques series in future.

Talking to established physiologists about the usefulness of microarrays, I find that opinions are generally polarised between love and hate, but the latter is probably far commoner. I understand this antipathy. As with most new technologies, as the price becomes accessible the lure of rapid publication due to the novelty factor induces many to jump on the bandwagon and the literature explodes with a plethora of original but not necessarily useful data. A period of critical appraisal usually follows where researchers begin to comprehend the pitfalls and limitations of their pet technique, followed by a period of readjustment and refinement. Microarrays have just about reached this stage, which is probably a good time to think about using them.

Is publishing a list of up- and down-regulated genes really of use? Surely the real power of microarrays is what they can reveal about underlying processes, information perhaps not obvious from searching the literature. If used judiciously, the data can launch your research into a whole new and unanticipated direction. For physiologists, who are mindful of the maxim that an organism is more than the sum of it parts, this should be a golden age of opportunity.

Patricia de Winter
University College London

Concepts in microarray data analysis Part I. Power, confidence, *P* values and the problem of multiple testing

Microarrays are becoming popular tools in many fields of scientific research, including physiology, but the large volumes of data generated pose a challenge for their analysis. In this new mini series of articles, popular methods of analysing such data will be explained. In the first of the series Patricia de Winter (below) deals with the problem of deciding which data are significantly different

The explosion in genomics research has opened up the possibility of analysing the expression levels of hundreds to tens of thousands of genes simultaneously in a single sample using microarrays. The first microarrays were glass slides spotted with DNA complementary to the sequences of interest, and identified mRNA transcript levels, but the technology has expanded within the last few years to include arrays that can identify DNA methylation, single nucleotide polymorphisms, microRNAs, phosphorylated proteins and protein–DNA interactions, to name a few applications. Gene expression arrays are still the most common and as their popularity has increased, the cost, once prohibitively expensive for most labs, has dramatically decreased. Due to the high cost of the hardware and the recognition that reproducibility is greatest when performed by specialised centres, most researchers now send their samples to a core facility or private company for processing. Typically the raw data files plus additional files of corrected, normalised data are returned to the investigator. Some centres offer limited statistical analyses such as returning *P* values with the normalised data at no additional charge.

So what is the attraction of microarrays? As microarrays probe an entire genome or process, they offer data that are unaffected by the researcher's bias of the effect of a treatment, disease or changes over time. Of the thousands of genes, proteins or other molecules examined in the microarray, a few dozen to a few hundred are typically

differentially changed in expression or status by the treatment. In the research setting, as opposed to the diagnostic setting, microarray data can be useful for generating hypotheses for further study. For the purpose of this series, the experimental conditions, such as disease status, application of a drug or compound, or the changes over time, will be called a 'treatment' and the genes, proteins etc. being investigated by the array will be called 'targets'.

When microarrays were in their infancy, researchers typically took the mean fold change of a treatment in one group *versus* another and if the changes were two-fold or greater, the treatment was deemed to have had a genuine effect. The obvious flaw with this method is that it does not account for the variability within the groups, and neither does it account for the number of samples in each group, so using a fold change alone does not give us enough information to enable us to judge whether the observed differences are real. Imagine that you have treated some cells with compound A and measured its effects on levels of gene B. You would take the mean and a measure of variability for each group and probably plot a graph with error bars in the first instance to see what the

Table 1. Use of guilt or innocence in a court of law (A) as an analogy for statistical error (B)

A

		True situation	
		Null is false	**Null is true**
Verdict	**Null is false**	Correct	Incorrect (type I error)
	Null is true	Incorrect (type II error)	Correct

B

		True situation	
		Guilty	**Not guilty**
Verdict	**Guilty**	Correct	Incorrect (innocent is convicted)
	Not guilty	Incorrect (guilty goes free)	Correct

data looked like, once summarised. If they looked interesting, you might apply a statistical test. You would certainly never simply plot the means, calculate the ratio of the two treatments and say "Oh good, it's bigger than two, gene B has changed in response to the treatment". So why was this acceptable for microarray data? The difficulty with microarray data is their multidimensionality; this makes them more complex to analyse. Imagine an array contains 30 000 targets. Let us suppose that a third of these are actually present in the sample, so we have 10 000 tests to perform. A *P* value tells us the probability of observing a particular result when the null hypothesis is correct. Therefore, if we performed 10 000 *t* tests, 5% (e.g. 500) would be declared statistically significant irrespective of whether they result from the treatment or not. "Ay there's the rub" – now we start to understand the problems of microarray data analysis.

Table 2. A, hypothetical data for the expression level of gene X in two groups of samples, untreated (shaded blue) and treated (shaded brown) and B, random resampling (rearrangement) of the same data for one permutation of the test

A

Sample ID Untreated group	Expression level (log_2)	Sample ID Treated group	Expression level (log_2)
i	6.3	vii	9.5
ii	6.5	viii	8.9
iii	5.8	ix	11.1
iv	6.2	x	9.8
v	5.9	xi	8.5
vi	5.6	xii	10.8
mean, untreated	**6.05**	mean, treated	**9.76**

B

Sample ID	Expression level (log_2)	Sample ID	Expression level (log_2)
i	5.9	vii	8.9
ii	11.1	viii	6.5
iii	5.6	ix	6.3
iv	6.2	x	10.8
v	8.5	xi	5.8
vi	9.5	xii	9.8
mean	**7.80**	mean	**8.01**

Power and statistical error

Before we go further, it is necessary to introduce the concept of statistical error. Type I error is claiming that the null hypothesis is incorrect when it is not and conversely type II error is claiming that the null hypothesis is correct when it is not (Table 1A). An analogy that is often used to illustrate these concepts is that of the possible outcomes in an English court of law (Table 1B). The *power* of a statistical test is its ability to determine that the null hypothesis is incorrect when it actually is, which, in other words, means minimising the chances of false negatives.

It is important to understand when correcting for multiple testing, that reducing type II error necessarily increases type I error and *vice versa*. Hence, reducing the number of false positives needs to be offset against the risk of consequently not detecting targets that are truly different between treatment groups. This balance between the two evils of statistical error may depend upon the application of the data. Consider, for example, a situation where microarrays are used diagnostically to detect tumour samples from normal tissue samples. In this case it would be disastrous for the patient if a tumour went undetected. Therefore reducing type II error at the expense of type I error is probably preferable.

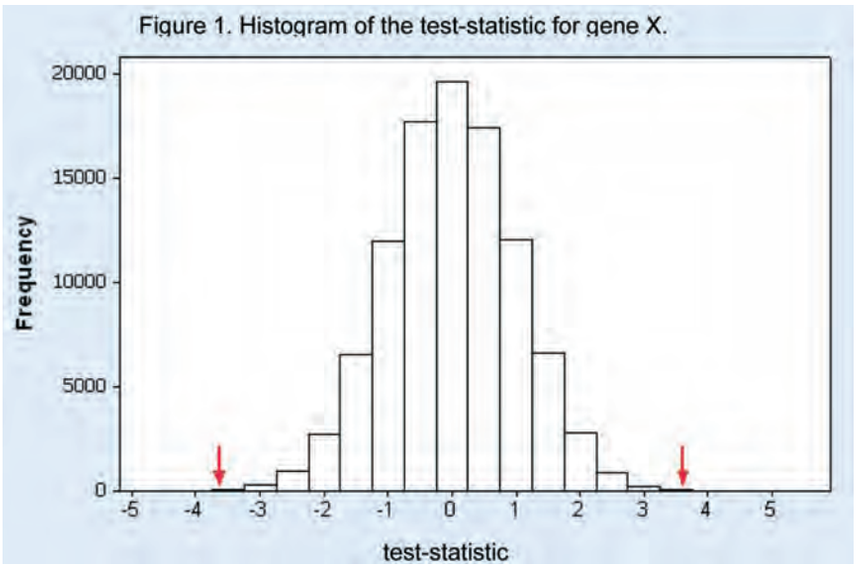
Which test of significance?

Firstly, what are the alternatives for discovering statistically different targets? The two methods in commonest use are currently *t* tests or permutation tests, both with a false discovery rate correction. As two excellent articles that discuss the *t* test have appeared in recent issues of *Physiology News* I will not dwell upon it in detail (Brown, 2008; Cahusac, 2009). Two points about the *t* test are important to note: that the data are assumed to

be normally distributed and that the variances of the two data sets are assumed to be equal. This can pose a problem for microarray data – with hundreds to thousands of targets it is not possible to test all of them for normality or equality of variances. To overcome the problem of non-normal data, the use of logged data is common. In log-transformed data, the effects of outliers are drastically reduced and so the distribution is usually, but not always, normalised. The variance problem is a little trickier. One can assume that the variances of the two independent groups are equal for all targets and apply *t* tests assuming equal variances (this is a bog-standard unpaired *t* test) or one can apply a *t* test assuming unequal variances for all targets. In this type of test the degrees of freedom are reduced and so it is more conservative, but the risk is a greater chance of type II error. With microarray data, the unequal variances *t* test is probably a safer bet.

If *t* tests cause problems for analysing microarray data, why not use statistical tests that make no assumptions about the population distribution, such as classical non-parametric tests? The answer is that one can use such tests, for example the Mann–Whitney test, in place of an unpaired *t* test. However, the argument against such tests is that they tend to be less powerful, that is they may fail to detect statistically significant differences. An answer to this problem is to use permutation tests. These are more powerful modern non-parametric tests that have increased in practicability with the increase in available computing power. I will use a simple example to demonstrate the principle of permutation tests.

Imagine that we have two groups of samples with six observations per group: the first set of samples are untreated and the second received treatment. For simplicity we will look at just one target and call it gene X (Table 2A). The null hypothesis is



that the expression level of gene X in the untreated group does not differ from the expression level of gene X in the treated group. If this null hypothesis is correct, then all the observations have occurred by chance and are not related to treatment, or to put it another way, any of the samples could have exhibited the same expression level of any other sample. So in the next step of the analysis we will do just that – we will reassign the expression levels randomly to all the samples. (Table 2B). Now imagine that we repeat this step say, 100 000 times (this is the bit where a powerful computer is needed). By chance, we will end up with many datasets that look nothing like the original and some that will look similar, if not identical. Next we calculate some property of the dataset, which we will call the test-statistic – in this example I will use the difference in means – for the original data and for all 100 000 permutations of the data. The test-statistic for the original data is –3.71 (6.05–9.76 from Table 2A). Now, if we plot a frequency distribution (histogram) of all the test-statistics (mean differences) that we have calculated, it would look something like Fig.1. The values –3.71 and +3.71 are indicated by red arrows. As I have access to the original data, I can tell you that there are 26 test-statistics that fall outside these lines (more extreme), although it is tricky to determine this from the graph. Therefore, the probability of our original data having been observed when the null hypothesis is correct can be calculated as 26/100 000 = 0.00026. This is significant at below the 0.1% level.

We now have a statistical test that does not depend on any distribution and we need not worry about whether the variances are equal. The permutation test can be run on thousands of targets at once

Table 3. Example of Benjamini and Hochberg's procedure for controlling the false discovery rate of an example data set of 200 targets in total. For simplicity, the six smallest *P* values are shown (see text for explanation)

Original *P* value	Rank	$\frac{\text{Rank}}{200} * 0.05$	Significant	Significant using Bonferroni
0.00003	1	0.00025	Y	Y
0.00008	2	0.00050	Y	Y
0.0001	3	0.00075	Y	Y
0.0007	4	0.00100	Y	N
0.0009	5	0.00125	Y	N
0.02	6	0.00150	N	N

and there is a software package, an Excel add-in, freely available to academic users called Significance Analysis of Microarray Data, or SAM for short (Tusher *et al.* 2001). The disadvantage is that it does require a hefty wedge of computing power – imagine running even 10 000 permutations for as many genes and you will appreciate why that is. My aged work PC could manage about 600 targets for 16 samples, but got resolutely stuck when I tried 27 000 targets. Still if you have a decent PC, and a modest number of targets, SAM works very well, and can even perform comparisons of more than two groups.

Correcting for multiple testing

I have thus far described how to get a probability value for each target using either *t* tests or permutation methods. We still remain with the problem of multiple testing, mentioned above. A statistical method that has gained much support is that for controlling the false discovery rate (Benjamini & Hochberg, 1995). Prior to this, corrections for multiple testing, such as Bonferroni's correction, concentrated on the number of false positives for *all* tests performed. Bonferroni's correction is simply α, usually 0.05, divided by the number of tests performed. It doesn't take a great deal of imagination to realise that this is far too stringent; if you have just 5000 tests, threshold *P* would have to be ≤0.00001 to find a significant difference in your list of targets. The false discovery rate (FDR) is a less conservative alternative because it corrects for false positives only among tests that are *declared significant*. I will deal with the FDR only briefly here because the next article of this series will examine it in greater detail.

In Benjamini & Hochberg's FDR procedure, the threshold *P* for each test is calculated as follows: first rank all the *P* values obtained from the significance test from lowest to highest, then, starting at the lowest *P* value, divide its rank (which will be 1 for the lowest) by the total number of tests and multiply by 0.05 (Table 3). Compare the result with the original *P* value. If the calculated value is larger than the original *P* value, then there is a significant difference for that target, and if the calculated value is smaller than the original *P* value, then there is no significant difference. Repeat for *P* value ranked two, and so forth.

Benjamini & Hochberg's FDR was a landmark innovation in the field of multiple testing and led the way for further refinements of the procedure. Later, Storey (2003) improved the power of Benjamini & Hochberg's FDR further and introduced the concept of the *q* value. The *q* value is often described as an adjusted *P* value, but this is technically incorrect, although it is used in a similar way to *P* values to determine significance. Storey himself (2003) describes it as an 'analogue of the *P* value'. It is Storey's version of the FDR, the positive FDR (pFDR), that is used by SAM to correct for multiple testing. Once the FDR is set to the desired level, SAM returns a table of genes and their corresponding *q* values.

One final important point to note about the FDR is that because the calculation of the expected number of false positive tests depends upon the number of tests performed, the initial selection of positive targets will affect the outcome (Larsson *et al.* 1995). For example, initial filtering of the data in a gene expression experiment to select the number of expressed genes will affect the FDR depending upon which threshold is set for initially deciding the fluorescence intensity that represents the baseline noise. In a gene expression study, for example, the investigator can decide to include genes if the fluorescence value exceeds that of the background for at least one sample, through to all samples. Clearly, if an inclusion criterion is set to count a gene as positive if expressed in at least one sample, then many more genes will be counted as expressed than if the threshold is set to count if the fluorescence exceeds background in all samples.

Finally, with a few caveats in mind, we have a list of targets that are likely to be truly statistically significant. This, however, does not imply biological relevance so will need to disregard targets that are statistically significant, but where the changes are too small to be biologically meaningful (see Cahusac, 2009, for a discussion of effect size). Conventionally, the cut-off for biological relevance for gene expression data is 2, but this may differ for other types of data. For example, the cut-off for microRNA data is 1.5. This is because much smaller changes in transcription levels are typically observed for microRNA array data, possibly suggesting that these non-coding nucleic acids are more tightly regulated. For other types of data I would suggest searching the literature to discover what is generally accepted.

Future articles in this series will cover hierarchical clustering methods, principle component analysis and multivariate regression. I welcome other suggestions and my contact details are available from the Members' area of The Physiological Society web site.

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I would like to thank Dr Peter Cahusac for his critical appraisal of this article and very helpful suggestions.

Letters from Japan 2 – Where is home?

As I sit at my desk in Okinawa I realise how 6 months in my new home have flown by. I returned yesterday from a trip to the UK and Ireland which encompassed the Physiology 2009 meeting in Dublin, visits to Newcastle and Manchester Universities and the all important reunions with family and friends. The trip made me think a lot about the situation I am in just now. As I prepared to leave Okinawa I felt almost anxious. The first 6 months here have passed in a flash, with exciting projects in the lab, a large number of international scientific visitors and also adventures exploring Japan. I haven't once felt 'homesick' for the UK. But what if going back would make me realise what I was missing?

The Haari Dragon Boat Festival in Okinawa May 2009. We had a team in the race.

I arrived, after a long flight, in Newcastle and went straight to meet with friends from my old lab. We all did our PhDs together and are like family. I was shocked at how emotional I felt when I saw my best friend. We talk online almost daily but seeing her in person was different somehow. I was even more shocked at how busy Newcastle felt and how tall everyone seemed! I settled back in easily after a few days in the UK but noticed some unusual things during my stay. I was shouted at on the train to London for talking quietly on the phone for 2 minutes to arrange my pick up at the station – I have never heard a raised voice in Japan. When people asked me a question I nodded and said 'hai' or 'daijobu' (Japanese for yes or ok) and I bowed when I thanked people which attracted some interesting responses. The funniest was that I kept trying to get through doors with clear signs on them saying 'Please use other door'. After noticing this happen a few times I realised that I have stopped looking at signs in Japan as I can't read what they say.

Me with my parents at my Graduation in Newcastle.

I spent time with my parents, friends and pets whilst I was back and it was great to spend time with people I know so well. I am starting to make good friends in Okinawa now but it always takes time. I attended my graduation for my PhD in Newcastle whilst I was home. Spending time at home, I realised how simple my life was in the UK. It is not that it is difficult in Japan, but with the language barrier and different culture you face more personal challenges every day. After a few months of being here I had stopped noticing but a break from it made me realise how much of a challenge life in a new culture can be, in the most positive way.

I then started to feel anxious about coming back to Japan, as I had about going back to the UK. It is a strange feeling as you are not sure where you belong. I wished there were 2 of me so I could be in both places. You'll notice I often refer to the UK and Okinawa as home. The internet makes the world a smaller place and it is easy to chat to people you left behind online, even for free, which wasn't as easy in the past. This definitely makes it easier to settle in a new place.

Visiting the things I miss most while back in the UK.

I got on the plane back to Japan with my anxiety and a few tears (I rarely cry so this was a big thing!). I boarded the flight and was greeted by the hostesses with a bow. I wandered around the airport in Nagoya waiting for my connecting flight to Okinawa. I noticed the beautiful details of the restaurants, shops, gardens in the airport. Everything seems so delicate and precious. I then got in my car and drove to work this morning in the sunshine with the roof down. A large group of Japanese school children walking along the pavement turned to me and waved with big smiles. The Japanese people are friendly and kind and welcoming, and I am glad to be back after all. Sitting back in the office I am excited to get back into the lab and do some experiments.

Sampling the local past-times... me paragliding from the beach.

The trip highlighted how much I have learned and changed during the first 6 months living in a new culture. I realise how lucky I am to experience this wonderful country and learn about it whilst working in an inspiring scientific environment.

Fiona Randall

A world-class user facility to solve the nation's complex problems – The Environmental Molecular Sciences Laboratory (EMSL)

EMSL enables high-impact science with its sophisticated suite of experimental and computational capabilities

The Pacific North West evokes images of vast rain-soaked forests interspersed with occasionally active volcanoes, so it may come as a surprise that about two thirds of the landmass of Washington State is desert. Nestled in the heart of Washington wine country near the Oregon border is the metropolis of Richland, Pasco and Kennewick, which over time have merged to form the Tri-Cities. The town owes its existence to the Manhattan project of the Second World War, where its remote location and the nearby Columbia River provided an ideal site for the Hanford nuclear plant where the plutonium for the atomic bombs was manufactured. The population boomed with the influx of workers, and although the Hanford plant is currently being decommissioned the Tri-Cities remains a vibrant metropolis, blessed with a sunny climate.

Richland is my wife's hometown and a couple of years ago during a lull in the Christmas festivities I was invited to visit Aunt Barb's workplace at EMSL as we shared science as a career. This visit proved to be a revelation since, although I had lived in Seattle for a decade and had visited the Tri-Cities many times, I had never heard of EMSL. A subsequent more detailed visit last summer granted me the opportunity for more detailed scrutiny of the facilities available at EMSL. The first impression of the place is that it cements the American reputation for doing things on a large scale, and puts to shame the parochial attitude of the British government to 'Big Science'. For example, there is a baseball square-sized room containing seven NMR magnets, of which one is a 21.5 Tesla monster that at the time of introduction was the most powerful magnet in the world. Also present is a recently upgraded supercomputer contained in a room the size of a tennis court. Whilst this equipment is a technophile's dream, its most impressive aspect is that access to the facility is available to scientists from around the world at no cost. In the following article, Mary Ann Showalter and Kristin Manke of EMSL describe the resources and objectives of this government-funded facility.

An introduction by Angus Brown

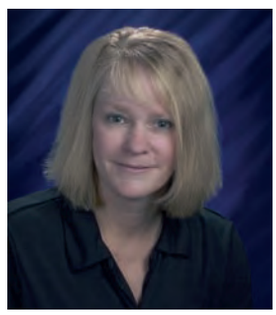
EMSL is located in the northwestern corner of the United States, in Washington State. The 224 463-square-ft (20 853.3 m^2) facility resides on the Pacific Northwest National Laboratory (PNNL) campus in Richland, Washington.

The EMSL facility

How do microorganisms exchange energy and electrons with minerals in soil, sediments and subsurface materials? What intricate steps are involved in creating hydrogen from water and other sources? How do microbial communities use transport proteins to adapt to seasonal changes and fluctiations in the levels of atmospheric carbon (yielding insights into global carbon cycling)?

These and multitudes of other complex research challenges are being solved by scientists worldwide using the unique capabilities and expertise at EMSL – the Environmental Molecular Sciences Laboratory, a US Department of Energy (DOE) national scientific user facility located on the campus of Pacific Northwest National Laboratory in Richland, Washington.

EMSL, a nearly 225 000-square-foot facility that houses more than 100 leading-edge capabilities in areas such as computation, mass spectrometry, nuclear magnetic resonance spectroscopy and microscopy, was the brainchild of the late William R. Wiley, former PNNL Director. Wiley once said "Problems don't come in small, unique, compartmentalized packages. We must recognize the interrelationships." In the mid-1980s, he began outlining his vision for a centre where scientists from around the world could gather to collaborate on molecular-level environmental, biological, chemical and computational research; in 1997, Wiley's vision became reality with the opening of EMSL to the scientific community.



Mary Ann Showalter.

Science that solves critical challenges

Fast forward to 2009. Enabled by EMSL capabilities, the scientific community comprised of researchers from all 50 of the United States and 30 countries – aptly called users – has published thousands of papers under their collective belts in high-impact, peer-reviewed scientific journals, including *Science*, *Nature* and *PNAS*. These users typically come from academia and the national laboratory system, with a number of others hailing from industry.

Their research during much of this time has focused around three major themes where EMSL is uniquely equipped – both capability and expertise wise – to significantly address complex challenges important to EMSL's client, the Department of Energy, and the nation:

Biological interactions and dynamics, which emphasizes a systems-level understanding of microbes and microbial communities.

Geochemistry/biogeochemistry and subsurface science, which focuses on one of DOE's singularly important challenges – the clean-up of legacy waste.

Science of interfacial phenomena (including a focus on atmospheric aerosol chemistry), which focuses on developing an understanding of molecular structure–function relationships at the atomic level that will allow precise control of interfacial activity and selectivity.

The result has been a lengthy resume of great science. A class of gold atom clusters – the first-known metallic equivalent of the buckyball – was discovered, with the potential to act as catalysts with novel chemical, magnetic or optical properties. A new class of proteins that transport carbon and nitrogen across cyanobacteria membranes has provided insight into nature's methods for carbon sequestration and nitrogen fixation. Carbon nanotubes were designed for use as biosensors to detect glucose, pesticides and nerve agents. Novel redox proteins located on the cell surface were revealed to facilitate microbial electron transfer to contaminants such as uranium and technetium, allowing formation of relatively immobile uranium dioxide and technetium dioxide–mineral phases with the potential to halt the migration of these contaminants through groundwater.

All great science enabled, at least in part, by EMSL capabilities and expertise.

What exactly makes EMSL unique?

Science that makes a great impact often requires access to unique, state-of-the-art capabilities. Unfortunately, with the rapidly growing demand for high-powered and high-priced instrumentation, 'unique' is often beyond the budget of a single university or institute. And while some user facilities house single, large instruments, known as 'big iron', EMSL provides the scientific community with access to a unique, integrated and collaborative problem-solving environment, bringing together extensive suites of instruments under one roof.

The ultra-high field of the 900 MHz NMR spectrometer has enhanced characterisation of liquid-state biological samples, enabled better characterization of solid-state insoluble proteins, and, for the first time, allowed measurements on a large class of nuclei in the periodic table that are described as quadrupolar in nature – the building blocks for catalysts and biomaterials such as metalloproteins

EMSL experts create new tools, tailor existing instruments, and upgrade the instrument collection to meet users' evolving needs. The unparallelled collection of instruments in EMSL allows users to tackle scientific challenges from all angles. For example, researchers are bringing together state-of-the-art conventional and developmental *in vivo* NMR techniques to study metabolism in live cells. The first application of this new integrated capability set is to study the metabolism of biofuel-producing microbes (Majors *et al*. 2008). Three of EMSL's flagship capability groups are described briefly here. More information on these and other capability groups available at EMSL can be found at www.emsl.pnl.gov/capabilities/instrumentList.jsp

Just one component of EMSL's suite of microscopes, the transmission electron microscope with capabilities for cryo-stage and tomography is used with biological samples involving morphological and immuno-cyto-chemistry studies, and it supports imaging of samples such as soft materials and polymers.

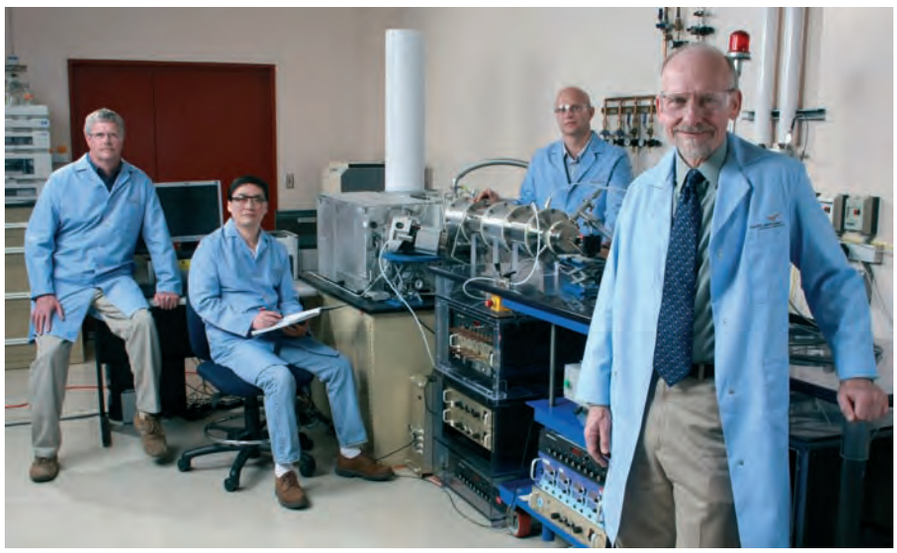
NMR spectrophotometers. EMSL's 12 NMRs, with fields up to 900 MHz (21 Tesla), allow scientists to study structure and function in liquid, solid and living samples. The lowest field (2 T) NMR is a horizontal system with a 300-mm-wide bore and custom-built gas imaging technology. Researchers use this system to observe air–water exchange in samples ranging from lung tissue to fuel cells.

The ultra-high field (21 T) NMR system is used to study difficult-to-observe metal systems in environmental clays and minerals, catalytic materials and membrane proteins. Experts at EMSL have built a wide range of probes for this 900 MHz NMR, and are continuing to build more. For example, EMSL experts used a recently constructed high-temperature solids magic angle spin (MAS) probe to study catalytic materials. Virtual NMR tools are also available so researchers can run samples and gather data on the system without incurring the expense of travelling to EMSL.

Microscopy. EMSL's array of microscopes (scanning probe, optical and electron) can characterize and analyse samples with nanoscale – and even atomic – resolution. EMSL's T-12 cryo-transmission electron microscope is equipped with cryo-stage and tomography capabilities to accommodate users' demands within the fast-growing field of biological imaging at the nanoscale. It provides detailed images of samples in a frozen, yet hydrated, state. It has ±70 deg tilt for electron tomography that allows three-dimensional reconstruction of an object to be achieved.

EMSL's focused ion beam/scanning electron microscope, known as the FIB/SEM, provides dimensional reconstruction of structures using electron backscattering and energy-dispersive x-ray analysis. This capability offers a cryo-stage for investigating soft materials, in particular, dynamic cellular processes.

Mass spectrometry. Because of the range of research conducted at EMSL, mass spectrometry capabilities are dedicated to different research areas. Specifically, capabilities are designated for proteomics research, aerosol particle characterization and ion-surface collision. For the proteomics research, EMSL's mass spectrometry resources include a 12 T Fourier-transform mass spectrometer upgraded with an award-winning ion funnel and additional quadrupole stages for enhanced ion transmission. EMSL also houses custom high-performance liquid chromatography systems for protein and peptide separation.



EMSL's suite of cutting-edge mass spectrometers has enabled several proteomic studies, including one by a research team from Oregon State University, PNNL and the University of California where scientists, for the first time, measured protein expression in microbial communities from the Sargasso Sea. Understanding how microbial communities use transport proteins to adapt to seasonal changes and fluctuations in levels of atmospheric carbon yields insight into global carbon cycling and could help in the design of strategies to address global warming. (Sowell *et al.* 2009)

Taking the uniqueness further: integrating computation with experiment

Theoretical studies often provide greater insight into experimental data – and the cornerstone of EMSL is to provide the user community with integrated experimental and computational resources. EMSL supports theoretical calculations, simulations and models with both computational hardware and software. One example involves a team of EMSL users from University College London, who combined EMSL's high-level theoretical calculations and laser-based experiments to customize surface structures on an atomic scale. Such structures have valuable applications in catalysis and microelectronics.

The centrepiece of EMSL's hardware is the newly installed Chinook supercomputer, a 163-peak HP teraflop system with 36.96 terabytes of RAM. One code commonly run on EMSL's supercomputer is NWChem, an award-winning software that applies theoretical techniques, such as Hartree-Fock and density functional theory, to predict the structure, properties and reactivity of chemical and biological species, ranging in size from tens to millions of atoms. For example, researchers are combining NWChem and the NMR capabilities at EMSL to derive a molecular theory that describes the electronic environment of the metal–amino acid motif, zinc coordinated to four cysteines.

However, not all theoretical studies require the power of a supercomputer. Smaller computational systems are also available. In addition, EMSL provides a Graphics and Visualization Laboratory for the analysis and display of complex data sets from both experiments and computer simulations. For those studies that would benefit from this laboratory and the supercomputer, the two are linked via a high-speed network, allowing both of the systems to work together on large-scale scientific applications.

A great proposal: unique systems to support high-impact science... at no charge?

Access to EMSL's cutting-edge experimental and computational capabilities is gained through a peer-reviewed proposal system, at no cost if research results are published in the open literature and acknowledge EMSL's contribution. Proprietary research is also conducted at EMSL, but on a full cost recovery basis.

Each year, EMSL sends out a call for proposals to the scientific community for research that fits under one of its science themes, for computationally intensive research, or for research that could be enabled for capabilities that are currently undersubscribed by users. Interested researchers are encouraged to identify the capabilities they wish to use (specifications of the instruments can be found on the EMSL website) and contact the EMSL staff member associated with the instrument to discuss the potential research before submitting a proposal via EMSL's user portal (https://eus.emsl.pnl.gov/Portal).

Recognizing researchers: EMSL rewards its users

EMSL is recognizing its active users as well as deserving post-doctoral fellows through new fellowship and award programs launched and implemented this year.

The Wiley Visiting Scientist Program recognizes, rewards and encourages distinguished scientists to come to EMSL for extended periods of time and make significant contributions to

the EMSL user program by providing input to and recommendations on the path forward for EMSL. Wiley Visiting Scientists can actively contribute to the success of EMSL by participating in partner proposals to develop new capabilities, mentoring EMSL staff and assisting in long-term facility planning.

The Wiley Research Fellow Program recognizes researchers who make significant contributions to EMSL outside of their individual research efforts. Wiley Research Fellows can actively contribute to EMSL decision-making processes by serving on advisory committees, participating on partner proposals for new capability development, acting as a scientific consultant for users, advocating EMSL and its capabilities in the scientific community, as well as assisting and supporting a broad range of EMSL user activities.

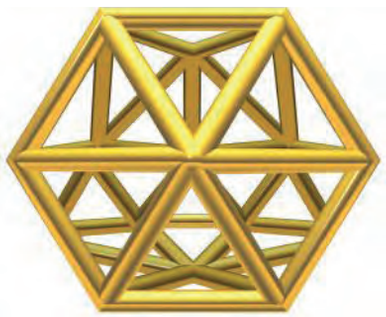
The William Wiley Post Doctoral Fellowship is designed to attract high-performing, newly graduated junior PhD scientists who have the potential to become full time scientific staff at EMSL.

In addition, EMSL's long-standing award program, the MT Thomas Award for Outstanding Postdoctoral Achievement, acknowledges the contributions of post-doctoral fellows who have used EMSL resources during the previous year. The award is named for M. Tom Thomas, a vital leader as EMSL progressed from concept to reality. Now in its thirteenth year, the program has recognised some early-career scientists who have, later in their careers, garnered prestigious awards such as the Presidential Early Career Award for Scientists and Engineers and who have made great contributions to high-impact papers published in journals such as *Science*.

For information about these programs, visit the website.

A home away from home

Just a half block away from EMSL is The Guest House at PNNL, an 81-room facility designed to make accommodation and travel to EMSL and other PNNL facilities more convenient – especially when experiments are conducted during out of office hours. Studios



A team of EMSL users from the University of Nebraska and Washington State University used EMSL capabilities to discover a class of gold atom clusters that have catalytic properties (Bulusu *et al*. 2006).

and one-bedroom apartments are available for the lone traveller, while six-, seven- and eight-room suites are offered for the research groups that travel together. For more information about The Guest House at PNNL, see www.pnl.gov/guesthouse/.

Looking toward the future

Because of the changing nature of the scientific endeavour, EMSL is dedicated to continually updating its capabilities to keep the facility at the state of the art. Thanks to President Obama's American Recovery and Reinvestment Act – also known as the stimulus plan – the Department of Energy has provided EMSL with $60 million to spend on refreshing EMSL's suite of instruments in the areas of microscopy, mass spectrometry, computation and NMR spectroscopy. This funding will allow EMSL to accelerate its original capability enhancement and equipment renovation plan from 2010 to the end of 2013 – and will result in a user facility that provides the scientific community with the highest-quality, most unique systems with which to perform their research.

By continually upgrading the capabilities at EMSL, the facility continues to offer researchers the uniquely equipped laboratories they need to change the game of science. With the energy and environmental challenges before the world today, this work has never been more important.

For more information about EMSL's science, capabilities, and resources, see www.emsl.phl.gov/

A collaborative, problem-solving environment

EMSL was designed to make collaboration an easy and natural part of the research experience. Meeting spaces and gathering spots are located throughout the facility. Scientists frequently gather around the whiteboards to discuss results. EMSL staff and users use these spaces for lunchtime discussions and gatherings, fostering communication and collaboration among scientists, post-doctoral fellows and graduate students. For example, through these interactions, students in the Summer Research Institute, a program focused on developing the next generation of interfacial and condensed phase scientists, met and collaborated with scientists, who later became part of the students' research projects and resulting publications.

Collaboration at EMSL, however, goes far beyond the architecture. When conducting research at EMSL, scientific users can also request consultations with experts on staff at EMSL. These scientific consultants can assist in designing experiments, setting up instruments, interpreting results, selecting additional experiments or establishing follow-on experiments. The consultations are offered at no cost. Further assistance is available through EMSL's Instrument Development Laboratory, which designs and develops much of the custom hardware and software at EMSL, and rapidly modifies or adapts users' systems as needed for frontier-advancing experiments.

Mary Ann Showalter
Kristin Manke

EMSL

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Medical testing – do we want more or less of it?

Parliamentary and Scientific Committee Meeting, 16 June 2009

This lively debate examined some of the rationales underlying current mass screening programmes in the NHS. The two invited speakers were Michael Baum (Professor Emeritus of Surgery and Visiting Professor of Medical Humanities, UCL) and Karol Sikora (Professor of Cancer Medicine and Hon Consultant Oncologist, Imperial College). Baum questioned whether there was too much routine screening for cancer in otherwise healthy patients, an approach that does little to help patients understand their real risk of developing certain cancers. Not all sarcomas detected at an early stage would eventually prove to be malignant: screening tended to be effective at detecting the more benign 'cancers', but less effective at catching the fast-growing, more malignant sort. So there was a danger that many patients were being alarmed at being told they had 'cancer', and then subjected to invasive treatments when their tumours were relatively benign. A few patients are genuinely saved by the process, but the downside of screening is false alarms, unnecessary surgery, over-diagnosis and insurance problems affecting a larger number. Screening is not necessarily a bad thing, but needs to be more targeted, including a risk assessment for patients, looking at details of their family histories and lifestyles, to deduce their likely individual risk. Patients falling into the low risk category could then be given lifestyle advice, with patients in higher risk groups being offered screening. Baum advocated that cancer screening should be approached more in the manner that the NHS screens patients for potential cardiovascular disease, with a more targeted risk-based approach.

Sikora emphasised how advances in technology had been driving many screening programmes, but warned that technology comes at a price – the right technology needs to be used with the right patient at the right time, otherwise it can be a waste of money. We need to move away from a one-size-fits-all approach, and develop better diagnostics more tailored to individual patients needs. Many existing tests for the early identification of disease are still too crude and generate too many false positives. More research needs to be done on understanding the genetic make-up of individual tumours to predict the real risks of disease progression for individual patients. Cancer is not one disease, and we need to be able to differentiate between the relatively benign tumours and those that are likely to become aggressive and invasive. An ageing population will naturally accumulate various diseases – the key will be better diagnostics, and thus more targeted treatments, to manage long-term chronic illness. Big Pharma is now becoming more aware of the need to develop tailored tests and drugs, and are changing their global business models. Translational research is the way forward.

The subsequent debate with attending MPs and Lords showed that they thought the points raised had huge implications for managing costs in the NHS. The overall conclusion was that patients don't need more testing, they need better testing, with tests conducted within a framework of an overall risk strategy programme, doing the right test at the right time. Diabetic and cardiovascular disease clinics were seen as models of relatively inexpensive risk management approaches that might be emulated in cancer and other areas.

Liz Bell

The Guild of Educators Seminar on Standards in Higher Education

London, 11 March 2009

This was a very interesting debate with Peter Williams, the Chief Executive of the Quality Assurance Agency for Higher Education (QAA for HE). HEIs are aware that quality and standards need to be managed carefully so that students can be offered a good educational experience and graduate with a qualification that is worth having. This is done through their own quality assurance processes and with the help and oversight of the QAA. We still have a genuinely world class education system but we cannot be complacent as competition from institutions abroad is hotting up. The sector has grown dramatically in the last 20 years, with an expanded university sector, and 650 000 HE qualifications were awarded in 2007. No UK HEI is state owned, all are still essentially independent, self-regulating, associations of scholars. Once an HEI is recognised there is no statutory procedure to take away its degree-awarding powers. Funding Councils are required by law to assess the institutions they fund, and some professional societies also accredit degrees to assess fitness to practice. HEIs are very vocal about the heavy burden of accountability, and the Government's Better Regulation Agenda supports moves towards a more risk-based and light touch QA.

The QAA defines academic standards as a pre-determined and explicit level of achievement that a student

must attain for the award of a qualification. Subjects now tend to have benchmark statements, something that was fiercely resisted by HEIs in the past, but is now generally regarded as desirable. The public want transparency especially now that they have to pay more for HE. There are some issues in quality assurance that do need to be addressed, for example the external examiner system coming under strain and worries about how to deal with plagiarism in an age when students can access vast amounts of information on the internet. Universities are also under pressure to work with employers to provide more work-based learning. The current degree classification system is probably eventually doomed for many reasons including its inconsistency within and between institutions, a tendency towards grade inflation, and its lack of international comparability. It will probably be replaced with a Higher Education Achievement Report (HEAR) providing detailed transcript information on students.

On the more general question of whether standards were improving or getting worse in HEIs, it was agreed that it was rather meaningless in that there are no reliable, directly comparable, data between different decades to support this, and in any case, standards must meet the needs of the present and not be fixed in eternity. Knowledge and Society both move on. A more meaningful question is to ask whether standards are carefully defined and meeting the needs of today's graduates and employers, and are the learning opportunities provided optimising the chances of students to meet these standards.

Liz Bell

International capacity building

On 2nd June 2009 we held an event on international capacity building issues in partnership with the Institute of Physics, Royal Astronomical Society and UNESCO. The event was attended by over 40 senior representatives from a broad spectrum of UK learned societies, and external organisations such as the Department for International Development (DFID), who engaged in a lively discussion, resulting in a long list of possible action points. These are currently being considered by a Steering Committee of the original organisers, which has now been expanded (following shameless talent spotting by me at the event), to include a mathematician and a nutritionist. A future article in *Physiology News* will report on these as our plans firm up. The article below was published by the Institute of Physics in their members' magazine, and we expect that other societies who attended the event will do likewise. A full report of the meeting, once it has been discussed and agreed with the participants, will be available from me (please contact me if you would like a copy: ebell@physoc.org). A journalist also reported on the meeting (www.scidev.net/en/news/developing-world-beckons-uk-learned-societies.html). What was interesting, and highly encouraging, is that The Physiological Society was extensively praised at the meeting by participants; some very eminent people from other societies have appreciated the lead that our Society has taken on this.

Liz Bell

Global role of science debated

Efforts to help developing countries to advance through building their science base should include elements of pure science as well as applied research based on each country's own priorities, according to Mike Cruise, chair of the international committee of the Royal Astronomical Society (RAS).

At a meeting on '*Capacity Building in the Developing World*', Cruise said that astronomy is 'a very powerful way of introducing people to the scientific method'. He said: 'When you go and teach children that you can predict a solar eclipse, that's the first time that they see a scientific prediction that comes true, so they start to see that science works. Then when you have an agricultural problem they believe that the scientific approach is the right one – previously they didn't.'

The meeting was organised by a small group of learned societies, including the Institute. It was held to exchange experience of capacity building programmes for developing countries, to examine the scale and status of these programmes in UK learned societies and to discuss possible benefits of coordinated action.

Hans Hagen, the Royal Society's senior manager of international grants, told the meeting that programmes funded by the society should be responsive to need. Its consultations seek to identify national research priorities such as agriculture or sanitation, he said. Peter Willmore of the Committee for Space Research added: 'The crucial thing is that these choices should be made by the countries that we're talking about, not by us.'

Opinion was divided on the best scale of project to attempt. Some attendees advocated joint bids for funding by several learned societies, while others claimed that 'small is beautiful'. David Elliot, the RAS's executive secretary, warned that big programmes come at the price of ceding control to funding organisations.

The Institute's director of communications, Beth Taylor, gave a talk on its Physics for Development programme. A large element of this has been providing experimental equipment to schools in countries such as Rwanda. Taylor said: 'In school, the time when I really understood things was when I saw the experiment working. That was what was missing from the schools in Rwanda.'

At the meeting, which was led by Liz Bell of The Physiological Society,

those attending agreed that the group should review opportunities for increased collaboration arising from the discussions at the event.

Chris White
Institute of Physics

(This article was first published in the IOP members' newspaper)

Young scientists condemn the use of homeopathy to treat HIV and malaria

When I was told about the 'Homeopathy for Developing Countries' conference in the Netherlands, I was appalled to discover that homeopathy is being promoted to treat malaria, HIV, TB, infant diarrhoea and influenza in developing countries. The Abha Light foundation in Kenya sells homeopathic medicines for malaria, diarrhoea and influenza; the Tanzania – Ireland Alternative Medicine (TIAM) project promotes homeopathy as a cost-effective treatment for malaria; Amma Resonance Healing Foundation (ARHF) promotes a remedy for AIDS. If homeopathy takes the place of effective treatment, lives will be lost.

The Voice of Young Science (VoYS) is a network of 500 early career researchers committed to the promotion of evidence-based science. Set up 6 years ago by Sense about Science, VoYS enables its members to gain experience working with the media and to take responsibility for correcting misinformation. We were shocked by the claims being made when we looked into this issue, and we all agreed that we had to take a stand. We discussed the best course of action, and it was stressed that given the urgent need for evidence-based medicines in developing countries, the situation is already incredibly difficult, without further confusion caused by misleading homeopathic claims. We decided to petition the World Health Organisation (WHO), which as yet has no clear guidelines on this subject, to issue a clear communication condemning the promotion of homeopathy for treating HIV, TB, malaria, influenza and infant diarrhoea in the hope that this would incite international recognition of its dangers.

We contacted like-minded early career scientists and doctors working in the countries most affected to add their support, and together we drafted a letter. Immediately our letter generated wide media coverage with articles appearing in the UK and around the world, particularly the South African press, and on blogs and forums. We have been contacted by doctors and medics expressing their concerns; they are eagerly awaiting a response from the WHO to give them support to challenge these practices.

While the WHO has acknowledged receipt of the letter, they are yet to publish a formal statement, and we will continue pursuing them until they do. Bringing this serious issue into the public eye is a great achievement. Even as young scientists we can make a difference and it is our responsibility to raise awareness of these issues.

If you would like any further information or would like to join the Voice of Young Science Network please contact Julia Wilson: jwilson@senseaboutscience.org

Harriet Teare
University of Oxford

Voice of Young Science media workshop June 2009

It was with keen interest that I read Ellen Forty's short report in *Physiology News* (PN75, Summer 2009) about the Science Media workshop she attended in March 2009, especially as I was travelling on a train to attend the same course myself, along with two other Members of The Physiological Society. This one-day course is sponsored by The Physiological Society, and is certainly doing a good job of engaging young scientists to at least start to converse with the media (even if it is in our own *Physiology News*). The day, as Ellen described in her article, was very interactive, with the chance to ask lots of questions to journalists and other media-relations professionals, including press officers, in order to prepare for interviews that might be due to our own findings, or being asked for our opinion as an expert on related topics (our Society, other learned societies and your university all have lists of experts – so try and get yourself on one). We were also urged to write letters to newspapers if we disagreed with science articles or even to get blogging (mentioning that we were a credible scientist).

Bill Wilkinson, one of the Physoc attendees, also clearly valued the day saying 'It was also an excellent opportunity to talk to the team at Sense about Science and discuss their various projects. From these discussions I learnt about their on-line teaching resources, which will be very useful, as I plan to give

some presentations in secondary schools in the near future as part of the "Researchers in Residence" programme'.

The Voice of Young Science is a very industrious and engaging network, which encourages scientists with all backgrounds to stand up for science, and to try and uncover the truth behind 'pseudo-science' in the press or in advertisements. 'Don't be scared' we were told, engage with the media, especially after you have prepared the three points you wish to get across in an interview. Knowledge Transfer and Exchange are becoming buzz words on grants, and universities are now recognising that Knowledge Transfer is vital and is becoming part of the promotion process, so now is the time to get involved with the media and the public. As I mentioned in my article in the same issue of *Physiology News* (Tomorrow's women, tomorrow's world), it is vital that we ensure that we have young scientists who are visible role models to excite and inspire the public especially the young. What better way than being on the TV, the radio or even in *The Sun*. I highly recommend this workshop – so watch this space for young physiologists getting air time!

Valerie Gladwell
University of Essex

Sense About Science campaign to keep the libel laws out of science

Some Members will probably be aware that the well-known British science writer Simon Singh is being sued for libel in the English High Court by the British Chiropractic Association (BCA). The lawsuit is over an article Singh wrote in the *Guardian* in which he criticised the BCA for promoting chiropractic treatment for certain ailments such as childhood asthma, where he argued evidence of efficacy was lacking. The BCA were apparently offered a right of reply by the *Guardian*, but chose instead to pursue Singh personally through the libel action.

The organisation Sense About Science has started a major campaign to protest at the use of English defamation laws to curtail scientific debate under the banner Keep Libel Laws Out of Science.

As part of this campaign, an online statement of support for Singh has now gathered more than 15 000 signatures. Among the first group of signatories are Clive Orchard, The Society's President, and past Presidents Colin Blakemore and Ole Petersen, together with many other distinguished scientists, writers and editors, journalists and public figures.

Part of the statement reads:

Freedom to criticise and question in strong terms and without malice is the cornerstone of scientific argument and debate, whether in peer-reviewed journals, on websites or in newspapers, which have a right of reply for complainants. However, the libel laws and cases such as BCA v *Singh have a chilling effect, which deters scientists, journalists and science writers from engaging in important disputes about the evidential base supporting products and practices. The libel laws discourage argument and debate and merely encourage the use of the courts to silence critics.*

The English law of libel has no place in scientific disputes about evidence; the BCA should discuss the evidence outside of a court room. Moreover, the BCA *v* Singh case shows a wider problem: we urgently need a full review of the way that English libel law affects discussions about scientific and medical evidence.

We urge Society Members who are interested in these issues to visit the site: www.senseaboutscience.org/freedebate

Standing up for Science Media Workshops

The Society is sponsoring Sense About Science's VOYS Standing up for Science Media workshops. These are for post graduates, postdocs or equivalent in their first job who want to get involved in public debates with the media and other organisations about science, particularly on contentious subjects. These workshops are free and application is by CV and covering letter to jwilson@senseaboutscience.org

The Society has a number of allocated places on the workshops, so please make it clear in your application that you are a Member to help secure a place. The next media workshop will be taking place in Edinburgh on 6 November. For more information please visit: www.senseaboutscience.org/voys

Sense About Science is an independent charitable trust that responds to the misrepresentation of science and scientific evidence on issues that matter to society, from scares about plastic bottles, fluoride and the MMR vaccine to controversies about genetic modification, stem cell research and radiation. We work with scientists and civic groups to promote evidence and scientific reasoning in public discussion.

100 years ago in *J Physiol*

The dissociation curve of blood

Joseph Barcroft & Mario Camis

J Physiol **39**, 118–142 (1909)

The paper by Barcroft and Camis deals with something instantly recognizable to anyone who has taken a physiology or medical degree, or taught physiology – the haemoglobin oxygen dissociation curve. However, those who merely know the curve from books might like to read the paper's experimental sections (and that of a shorter paper that follows it by Barcroft and Ffrangcon Roberts) to see the heroic efforts necessary to make these measurements a century ago.

Joseph Barcroft, though he became one of the great men of English physiology, was not strictly an Englishman. Born to a Quaker family in County Down in what is now Northern Ireland, he arrived in Cambridge aged 21 in 1893, remaining there – excepting the two world wars – until his death in 1947. His first notable work was on tissue O_2 consumption; Barcroft perfected the methodology for getting reliable measurements of tissue O_2 uptake, and his seminal work on this, published in three papers on 'The gaseous metabolism of the submaxillary gland' in *J Physiol* in 1900 and 1901, made his reputation. He later applied the same techniques to various other organs with a series of eminent collaborators, including Ernest Starling (pancreas) and WE Dixon (heart). Barcroft was also JS Haldane's partner in the development of the Haldane apparatus, described in 1902, which allowed accurate measurements of dissolved O_2 and CO_2 in small blood samples, and remained a standard piece of lab equipment at least until the 1970s.

The 1909 paper represents one instalment of Barcroft's most lasting scientific preoccupation, haemoglobin. In his excellent Oxford DNB entry on Barcroft [1], John West summarises these interests as follows:

'Aspects which [Barcroft] studied included the effects of temperature, carbon dioxide pressure, acidity, salts, dialysis, diet, exercise, and high altitude. The last prompted him to participate in two high-altitude expeditions, one to Tenerife in 1910 and another to Monte Rosa in 1911.' (Barcroft later led a further altitude expedition to the Peruvian Andes in the early 1920s.)

The 1909 paper is unremarkable at first sight, being a series of painstaking measurements of the O_2 dissociation curve of haemoglobin in various salt solutions, and also of blood. However, the paper has a secondary fame, since its dissociation curves were those later used by AV Hill to test his derivation of the Hill equation, presented to the Society a few months later, on 22nd Jan 1910 and published in the *J Physiol* Proceedings [2]. As Hill writes:

'Our [i.e. Barcroft and Hill's] work led me to believe that the divergence between the results of different observers [on the Hb dissociation curve] was due to an aggregation of the Hb molecules by the salts present in the solution... To test this hypothesis I have applied it to several of the dissociation curves obtained by Barcroft and Camis with Hb in solutions of various salts...'

The Barcroft and Camis paper is also notable for the lucid discussion which the authors give of the implications of the haemoglobin dissociation curve for tissue oxygenation, a section obviously informed by Barcroft's work on O_2 uptake.

'It is clear that blood containing less than 70% of its usual quantity of O_2 and circulating at the usual rate will fail to satisfy the [O_2 requirements of] muscle. Therefore if the muscle is not to suffer from deficiency of O_2 the circulation must quicken and the muscle must either receive blood at the expense of other organs or extra work must fall upon the heart. We may push our enquiry somewhat further and say a word about each of these alternatives. The heart, itself a muscle, is at the same initial disadvantage as the rest of the musculature of the body and therefore can only ward off its own [hypoxia] at even its normal rate of working by increasing its blood supply... to require increased work of it is therefore to set up a vicious circle. As regards other organs we need only mention two, the kidney and the brain. These are probably even more sensitive to want of O_2 than muscle...

In all these cases the tension of O_2 in the venous blood might be and probably is raised by local vascular dilatation. It is hardly necessary to point out how great would be the strain on the vascular system of endeavouring to maintain the blood-pressure [under these circumstances].'

I imagine many a modern physiology teacher would be gratified if a student of a century later showed anything like this degree of 'integrative understanding'.

In addition to his interests in haemoglobin, O_2 delivery and altitude physiology, Barcroft – who became an FRS in 1910 – pioneered other areas, most famously fetal physiology and metabolism. He died, garlanded with accolades and still busily working, in 1947. His elder son, Henry Barcroft (1904–1998) became a famous circulatory physiologist and also an FRS.

Mario Camis (1878–1946), Barcroft's co-author, was a visitor from the University of Pisa who spent 1908–9 in England, first at Cambridge with Barcroft and subsequently in Sherrington's laboratory in Liverpool. Camis returned to Italy to become a founding father of Italian neuroscience, and did notable work on the brain projections of the vestibular system. In 1939 Camis was evicted from his Professorship in Bologna, because of his Jewish ancestry, following the passing of Mussolini's racial laws. He became a Dominican monk and left Italy to teach science abroad, never returning to research.

After Barcroft's death, a Haemoglobin Symposium in his honour was held the following year in Cambridge, attended both by those who had known Barcroft and by a roll-call of haemoglobin luminaries. The full text of the Symposium volume can be found online. AV Hill in his contribution recalled Barcroft and Camis' work of 40 years earlier:

'My first memory of JB was about 1908 or 1909... Thereafter I saw him continually in that old laboratory behind the green baize curtain [Barcroft's lab space was a corner of a room divided off by the curtain]... I remember [an] accident that... happened to an apparatus laboriously built up. Carelessness by another brought it all crashing to the floor. Instead of using sailor's language [Barcroft was a keen sailor] JB looked at it quietly and said: 'Oh, well, we'll just put it up again.' That was characteristic of the patience of his work... I well remember... various of his colleagues and pupils shaking blood gas apparatus endlessly in baths in the chemical laboratory just down the passage. The one I remember best was Camis, because of his short legs: these required that he should stand on a stool by the bath. When I think of blood gas apparatus, the picture of Camis comes back to me.'

Austin Elliott

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Cash in the time of swine flu

Recently a heinous financial tragedy befell my beloved wife Professor Cressida Cormorant – her repeated requests for research funding were refused. Cressida specialises in the psychopharmacological influences maintaining class hierarchies and patriarchal dominance in the work of Jane Austin. You may have recently watched a recent Channel 4 adaptation of her work 'Incense and Insensibility' which explored the synergistic effects of met-amphetamine and lysergic acid in Late Georgian courting rituals.

Cressida, being grant less and therefore being 'without value in western society', was then summoned by her head of department and subjected to a humiliating dressing down. Unfortunately Cressida, being a sensitive soul, was only able to transcribe some of the more repeatable things the professor said.

'Your problem is you don't know how to play the game.'

'These days it's not enough to be on Channel 4, research is like a politicised version of the bloody fashion industry.'

'You need to get a bit devious and a bit real.'

'The problem is that your research perfectly fits the weirdo political landscape of the 1960's. Haven't you heard of the banking crisis? This is 2009, everybody is bankrupt. When there is no money, funding bodies need to justify spending in a very disingenuous manner. You need a baited strategic hook, a mechanism to get a funding body to cough up the cash. Your research – it's not biomedical, strategic, applied or translational. You just don't seem to have developed the capacity to bulls**t and adapt your research proposals around the fashionable hypotheses of the age. So what if Mr Darcy takes LSD and Anne Elliot has hissy fits because she mixes laudanum with her magic mushrooms. What relevance has this got to do with Gross Domestic Product, Living with Environmental Change, Biosecurity or any other stupid government initiative?'

'Emerging diseases, that's a good one. It makes the government look like they actually care about what happens to the general population. Look at Prof Reg Wentworth, in 2007 he got three grants just for signing up to a bird flu initiative, but he's never seen a chicken cough, sneeze or have a runny nose in his life.'

'Tragic-looking children's diseases, that's another one. Can't you just apply for some money to work on that? Just when your average politician is about to do something really mean and vindictive they pop round to a hospital and cuddle a tragic looking child. They love it – makes them look compassionate, especially when the pictures end up in *Hello* magazine.'

The professor then gave my traumatised wife Cressida an ultimatum.

'You have two choices. It's either you make your research appear "translational" and spin your research proposals to fit fashionable strategic initiatives, or you take voluntary redundancy.'

Cressida was initially distraught but has recently recovered enough and has applied for three 'bio-medically' relevant grants that fall under the strategic funding priorities of the Wellcome Trust, the BBSRC and the MRC.

'Pride and Pestilence'

In this proposal we examine the compelling hypothesis that the genomic sequence of H1N1 swine flu is not a uniquely modern phenomenon, but merely represents a pastiche of elements of the earlier neo-classical Georgian influenza genome. 3 years, £450,000, (+£500K because the Prof needs a really flash Deep Sequencing Platform for something else). **Emerging Diseases – interdisciplinary networks and programmes. The Wellcome Trust.**

'The Northanger Abby Synthetic Biosciences Consortium Proposal'

Late Georgian Britain was a time of great change, innovation and political ferment. In this proposal we aim

to examine the irrational Georgian fear of the synthetic from *Persuasion* to Mary Shelly's *Frankenstein*. The translational applications of this grant are sociological and should enable the widespread introduction of synthetic biology into 21st century Britain with minimal public disquiet. 3 years, £500,000 (we apologise for the grant title but we thought if the BBRSC turned it down we could change a couple of paragraphs and resubmit it as a Medical Research Council Industry Collaboration Award). **Synthetic Biology. BBSRC Strategic Research Priorities**. (NB Personally I have always been wary of this, being of the view that the inevitable consequence of experimenting with synthetic biology is the sudden appearance of David Milliband. But! It's money).

'Complex Social Interventions and Late Georgian Reproductive Success'

In this grant proposal we intend to map a complex range of social interventions underpinning reproductive success. We believe it to be an excellent grant proposal in that it contains a complete range of disingenuous references to human health and disease. We have even managed to include the phrase 'Regulating social and reproductive success. The aversive social milieu and epigenetic modification of genomic sequences' in order to make the grant appear even more medically relevant, transferable and timely. 3 years, £450,000. **Methods Research for Complex Interventions. MRC Strategic Priority.**

Pride and Pestilence may be adapted for Channel 4, as a man with a disturbed personality. I am particularly looking forward to the scene where Mr Darcy succumbs to Georgian swine flu.

Keith Cormorant

Where does your pound go to?

Every time you register for the Society's Main Meeting and even when you get there, you are asked for £1 to buy a raffle ticket. It is a small amount and most people don't give it a second thought. But where does your money go and what is it used for? Thelma Lovick talked to David Brown, Chairman of The Physiological Society's Benevolent Fund, to find out.

David Brown (DB) Your pound is used to help people who are physiologists or who are in some way related to physiology departments in the UK who find themselves in unforeseen necessitous circumstances. It is rather like an old fashioned charity to look after impoverished people. The idea is to help people quickly and easily in a small way to see them through a difficult time.

Thelma Lovick (TL) What sort of people are we talking about?

DB They don't have to be card-carrying physiologists. In fact, they tend to be people like technicians or other support staff. Your average physiologist has a reasonable salary and a good pension so most of life's necessities are provided for. But there are exceptions. For example, one very well known physiologist died suddenly and because he originally came from abroad, had never entered into the Government's pension scheme. Consequently when he died his wife had no immediate source of money at all. The Ben Fund was able to provide her with a sum of money to help her through a rather difficult time until she could engage support from social services etc.

Another example was after the London bombing in July 2005. A cleaner for one of the physiology departments was blown up. The family, of course, were extremely distressed but they also had some immediate costs to meet. We were able to generate a small sum to help tide them over and they were very grateful for that. But it's not just the money. In cases like this, it was the recognition that they were someone who in their own way was helping physiology, by underpinning what everyone else was doing.

Those are examples of one-off cases but there are instances of more ongoing activities that the Fund supports. A technician in one department has a very disabled child and the family are on tap all the time to provide the long-term support that is needed. For the last 3 or 4 years we have given £1000 to enable them to go on holiday and take along the grandparents to help with the care,

The Ben Fund enabled Tom's grandparents to join the family on holiday and provide respite for the rest of the family by looking after him.

whilst the parents get a bit of a break. This is a situation where Social Services can't do anything to help but the Ben Fund can.

TL So what you're saying is that the Ben Fund can step in to fill a need that can't be met elsewhere. How do you find out about deserving cases?

DB It's very rare that people in distress contact the Ben Fund themselves. The key is that you need to have people in physiology departments who recognise a problem. These are the people who must write in and approach the Fund. So really one wants to appeal to all physiologists to keep their ears to the ground and contact us to see if we can do anything to help. And I should emphasize that we can respond very quickly. The Trustees get together via e-mail and with luck, if we are all around, we can make a response within a couple of days.

TL What proportion of requests are you able to grant?

DB Quite a high proportion actually, because most requests are very reasonable.

TL But surely there must be times when you can't help?

DB Well, yes there are. We had a request recently for 'fill in' support for a PhD student whose funding had come to an end. We can't support that sort of thing. Another request that we had a bit of a tussle with was for someone with colon cancer who wanted a drug that was not approved by NICE. There were several issues there. We wouldn't have had enough money to pay for continued treatment, if it had shown signs of working. Also we didn't know whether this drug really was effective. It turned out it wasn't. And then there was the issue of whether we should be bypassing what the rest of the population has to put up with. So there are limits to what we can support.

TL Tell me a bit about the history of the Ben Fund.

DB. It's a separate charity from The Physiological Society itself, although The Society administers it. The Fund was set up in 1976 '*for the purpose of assisting Members of The Society and staff and former staff (who by the nature of their employment can be considered to have contributed to the advance of physiology) employed at teaching, research and industrial establishments who are in necessitous circumstances and their dependants*'. There are about half a dozen Trustees (basically Society Members) plus two *ex-officio* members of Council such as the Treasurer.

TL Does all the income come from raffles?

DB. Oh no. The raffle is a relatively small (though important) part of our income, which is generally round about £4000 a year, plus investment income. Most of it comes from donations, sometimes as direct debits or standings orders or sometimes just one-offs. People might send in a cheque for £25 or £50 or something like that.

TL. I presume this can all be done under Gift Aid?

DB Yes, it's best done under Gift Aid, as in this way The Society can claim back the tax already paid. One nice gesture that Retired or Honorary Members can make, once they no longer have to pay an annual Society subscription, is to gift all or some of that saving to the Ben Fund. In fact, we're very keen to encourage this. It's a nice way to give something back to physiology.

For information on how to make a donation to the Ben Fund under the Gift Aid scheme contact Liz Bell at The Society's office (ebell@physoc.org).

(Note: all cases are treated confidentially but some beneficiaries are prepared to share their story to publicise the Fund.)

The raffle at the Dublin meeting raised over £320. The prize, a Fortnum and Mason's hamper of goodies, was won by Bob Banks at Durham.

1st Undergraduate Physiological Sciences Conference (UPSC)

Saturday 14 November 2009, Keble College, Oxford

UPSC is a new initiative launched by The Physiological Society to provide a forum for undergraduates with an interest in physiology.

The organisers of the 1st UPSC, The Oxford Physiology Society, would like to invite all students currently studying for an undergraduate degree in physiological/biomedical sciences to take part in this exciting new event. The day is designed to attract students with a broad range of interests.

We are proud to announce that the keynote lectures will be given by:

Denis Noble (University of Oxford)
Julian Paton (University of Bristol)

Apart from the lectures given by top-class researchers, the programme will include:

– students poster session

– a talk about PhD opportunities

– careers session featuring a CV clinic

– formal dinner with the speakers (optional)

Participation in the poster session is optional but strongly encouraged, and there will be an award for the best poster presented. Details are available on the website (see below).

All delegates from outside of Oxford are encouraged to participate in a 'buddy scheme' through which they will be assigned an Oxford student to provide them with useful information and, where needed, arrange accommodation for the night.

Travel grants to attend this conference are available to Student Members of The Physiological Society.

UPSC gives undergraduates a chance to:

– discover cutting-edge science

– gain experience in presenting their work

– explore career opportunities

– make friends and have fun!

For further information and to register, visit: www.physoc.org/upsc

International Society for Autonomic Neuroscience (ISAN) Congress, 2009 Symposium: Advances in sympathetic junctional transmission

Friday 4 September 2009, Sydney, Australia

Invited Speakers

James Galligan
William Dunn
Rohit Manchanda
Ian McGrath (UK)
J. A. G. Kennard (UK)

The generous support of The Physiological Society in supporting this symposium is gratefully acknowledged. The conference web site is: www.iceaustralia.com/isan2009/

British Science Festival (5–10 September, Guildford, Surrey)

The Physiological Society are supporting 'Brain Matters' at the forthcoming British Science Festival (see opposite). The hands-on workshop will take place on Saturday 5 September between 1 and 6 pm on Guildford High Street. It is open to everyone and is free to attend, so please come along.

Brain Matters is part of a wider programme entitled 'Discover Biology', which is supported by the Biosciences Federation and the Institute of Biology.

Brain Matters will engage people with all aspects of brain science, increasing knowledge about how brains can be protected from injury and disease, and enabling an informal forum for dialogue between families and neuroscientists. Interactive exhibits will appeal to a range of ages. Alongside the activities there will be a 'meet the scientist' event, so that parents and children can sit and talk informally with scientists while other family members are using the exhibits. This will ensure festival goers of all ages are engaged.

The Festival will be joining in the national celebrations of Darwin200 marking 200 years since the birth of Charles Darwin by exploring his scientific ideas and the impacts they made.

This year, The Society held an open competition for one of our undergraduate members to attend the full week of the Festival, supported by an Undergraduate Bursary. The recipient of the bursary was Freya Hopper from the University of Oxford.

More details about Brain Matters can be found on our website at: www.physoc.org

Biosciences Foundation–The Society of Biology

Richard Dyer.

There is excellent progress towards the integration of the Institute of Biology (IoB) and the Biosciences Foundation (BSF). The formation of the Society of Biology has been approved by Privy Council, and the Society will take on the integrated roles of the IoB and BSF from 1 October 2009. Before this date the assets of the BSF will be transferred, and shortly afterwards the BSF will cease any active existence. All members of the BSF and IoB will be members of the Society of Biology.

This important realignment, that I am confident will benefit biology enormously, has only occurred because of the strength and influence that the BSF acquired in recent years. This position, of course, derived entirely from the strength of the Member Organisations and the Member Organisations will have a central role to play in building the Society of Biology.

The President, Honorary Treasurer and Honorary Secretary positions are appointments of Council: Dame Nancy Rothwell will be the first President, William Marshall has been appointed as the Honorary Treasurer and David Coates as Honorary Secretary.

The current Interim Council (IC) will form the basis of the new Council, with a managed transition of the current members to the new profile of elected and appointed members from the two colleges (Organisational and Individual). Council members will be elected by the Society of Biology membership.

The CEO of the Society of Biology has been appointed and should be announced very soon. Competition for the post was very strong: all interviewed were excited by the vision that has to be delivered.

Personally, my work with the BSF has now come to an end. I leave, at the end of this week, with some sadness because the BSF has introduced me to many new organisations and interesting people – which I have very much enjoyed. For me it has been an enjoyable and stimulating 43 months. Emma Southern is now Chief Operations Officer (COO) for the BSF. Many of you will have discovered already that she is more efficient than I am: our organisation will be in excellent hands for the next couple of months.

It is important that our members contribute their views, ideas and questions about the Society of Biology. You can find out more at the temporary website: www.newbio.info. Please send any comments and thoughts by email or by adding to the blog.

Richard Dyer

The Journal of Physiology

Experimental Physiology
Translation and Integration
A publication of The Physiological Society

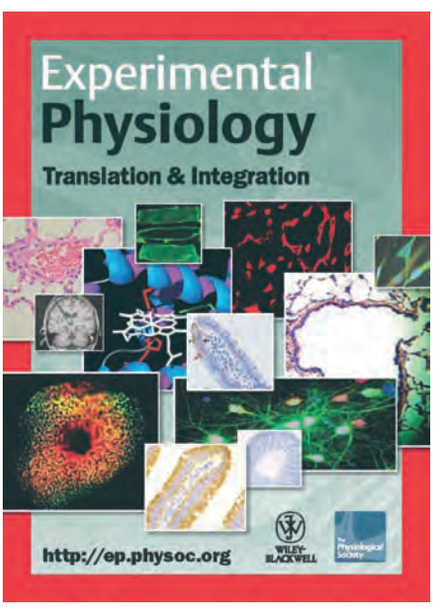
Impact factors and beyond

The 2008 impact factors (IF) released in June have remained essentially unchanged for both Society journals. *The Journal of Physiology*'s IF rose slightly from 4.58 to 4.60 while *Experimental Physiology*'s IF was marginally down from 3.01 to 2.91. This year, few of the journals in the Physiology list have shown marked changes in the IF, with the average change from last year's IF being less than 0.1.

As part of a general strategy to publish high quality research articles, the journals continue to focus on the need to maintain a competitive IF in order to attract good papers. In response to a question from the floor at the Society AGM in Dublin about the 'undue' importance accorded to the IF, which ignores papers that take longer than 2 years to accrue citations, William Large (Editor-in-Chief, *J Physiol*) commented that *The Journal of Physiology* aims to publish only highly influential papers and therefore early citation of papers is an important consideration. This year for the first time the 5-year impact factor is included in the citation metrics and, in general, variation from the 2-year number is under 10%, indicating that the percentage of 'slow burner' papers is very low in most physiology journals.

While both journals recognise the importance of the IF as a litmus test for authors choosing where to publish, there are other indicators of journal health. Submissions and downloads are also key metrics. Submissions to *The Journal of Physiology* have remained steady over the past year, even though *The Journal*'s acceptance policy has become stricter. *The Journal*'s online readership, measured as downloads of articles, is also robust, rising by 12% in 2008 to just under 4 million downloads.

At their recent Board meeting the Editors of *Experimental Physiology* considered measures to regenerate the upward trend in the journal's impact factor but remained confident in the underlying health of the journal as demonstrated by the enormous and sustained increase in downloads (from 66k in 2004 to over 800k in 2008) and the continued increase in submissions.



New Editors

Jeffrey T. Potts

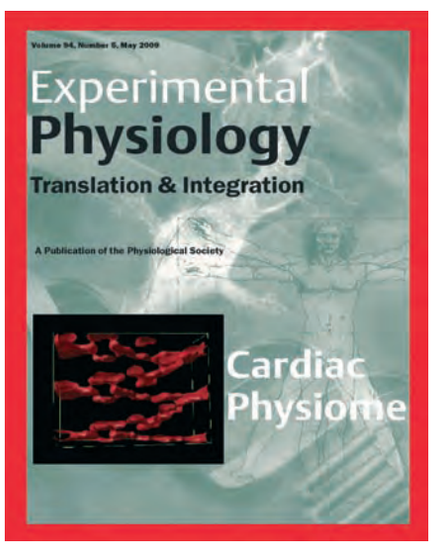
Jeff received his PhD in physiology from the University of North Texas Health Science Center at Fort Worth in 1993. He completed postdoctoral training at the Johns Hopkins University School of Medicine and the University of Texas Southwestern Medical Center in Dallas. Currently, he is an Associate Professor in the Department of Integrative Physiology at the University of North Texas Health Science Center. Jeff's research has focused on neural mechanisms that control the cardiovascular system during exercise. Current studies are addressing mechanisms that modulate synaptic function in homeostatic brainstem circuits controlling blood pressure and breathing.

John Osborn

John received his PhD in physiology from the Medical College of Wisconsin in 1986 under the tutelage of Allen Cowley. Subsequently, he conducted his postdoctoral studies with Lawrence Schramm in Biomedical Engineering at Johns Hopkins School of Medicine. John joined the faculty of the University of Minnesota in 1988 and currently holds the rank of Professor in the Department of Integrative Biology and Physiology. He was appointed as the Marvin Bacaner Endowed Chair in Cardiovascular Physiology in 2002. John's research focuses on the role of the nervous system in the long-term control of arterial pressure and hypertension. John is currently the Director of the Neurogenic Cardiovascular Diseases Consortium, a multi-institutional collaborative team in the US, investigating the central and peripheral neural mechanisms linking sodium retaining hormones, dietary salt and hypertension in animal models and humans.

Experimental Physiology sponsored a reception at the Cardiac Physiome workshop held in Cambridge 20–24th July (above).

Copies of the May Cardiac Physiome themed issue (right) were made available.



Experimental Physiology posters and 2009/10 wall planners are being sent to *EP* authors and reviewers. If you would like one too please send your name and address to ephjournal@physoc.org

The Journal of Physiology Symposia 2009

Advances and hold-ups in the study of structure, function and regulation of Cys-loop ligand-gated ion channels

Friday 16 October 2009

At Neuroscience 2009, Chicago, USA.

For full details of this, and other symposia visit http://jp.physoc.org

Today's neuroscience, tomorrow's history

The Wellcome Trust Centre for the History of Medicine at UCL has recently completed this major project, headed by longtime Phys Soc archivist Tilly Tansey and Les Iversen, which is now live online at:

www.ucl.ac.uk/histmed/audio/neuroscience.

The site offers extended interviews with a range of eminent figures in neuroscience, covering their lives and careers. Among those interviewed are Geoff Burnstock, Alan North, Ann Silver and Salvador Moncada. All the interviews are available either as downloadable podcasts or (via Youtube) video clips. The site is already proving popular, topping UCL's podcast download statistics. A more extended review of the site will feature in the next *Physiology News* – but in the meantime, do browse the site, which is full of fascinating material. For instance: did you know Geoff Burnstock's first published paper featured a fish and a condom?

IUPS and downs

I doubt The Society has any regrets (yet) about the optimism that led to its bid in 2005 for the XXXVII IUPS Congress to be held in Birmingham in 2013, 20 years after the XXXII Congress in Glasgow. None-the-less, a tale or two from past Congresses may concentrate the collective mind. No matter how exciting the science, recollections can be coloured, for good or ill, by practical issues. For the record: 1965 Tokyo, 1968 Washington, 1971 Munich, 1974 Delhi, 1986 Vancouver, 1989 Helsinki, 1993 Glasgow, 1997 Leningrad, 2001 New Zealand, 2005 San Diego.

Glasgow

Many Members, whether or not wearing an organizers' hat, will have varied memories of the 1993 Congress in Glasgow. Cecil Kidd, who chaired the Publications Committee, calculated that the Programme and Abstract Books (a separate one for each of the 5 days) totalled over 7.5 million pages. Not surprisingly, deadlines were alarmingly tight but Aberdeen University Press miraculously delivered everything on time to the Scottish Exhibition and Conference Centre in Glasgow. Here a team was waiting to stuff the Congress bags overnight ready for Registration next day on Sunday 1 August. So far so good except there was no sign of the bags due to come from Cambridge University Press. Anxious calls to the Press (a Saturday afternoon, mobiles still in their infancy) confirmed that the bags had indeed been dropped off at the SECC – there was a signed delivery note to prove it. The signatory was traced to the Catering Department where the bags were rescued from the Nescafé cartons in which CUP had packed them. (As an aside, the Congress literature and promotional handouts weighed about 4 kg and the CUP bags had to be supplemented by strong plastic bags bearing the Congress logo.)

And one small hiccup on the opening morning – the main area of the SECC was partitioned off into a number of adjacent lecture theatres served by a common electricity supply. Several were plunged into darkness when David Whitteridge caught his foot in a cable while introducing the first speaker.

Ann Silver

Hopefully more IUPS memories will follow in future issues. Perhaps there are other physiologists with useful memories to share.

Luis Silva-Carvalho

1954–2008

It is with great sadness that I report the death of Luis Silva-Carvalho on 20 October 2008. He had been diagnosed with pancreatic cancer some 6 months earlier and faced his illness with courage and a full understanding of the prognosis. His strong religious convictions and his close and devoted family were consolations for him. His wide circle of friends and colleagues, both from Portugal and internationally, also provided emotional support. His pride in his immediate family – Ana, an ophthalmologist, who had studied with him in Coimbra, and his two sons, Felipe, a psychiatrist in training, and Jaime, a computer-science undergraduate – was always evident and he was deeply involved in their careers.

Luis joined my laboratory at the Royal Free Hospital School of Medicine in 1989. He caused an initial stir as he appeared formal in an environment of casual irreverence. This resulted from his medical training and the relative conservatism of Portugal. It was, however, a contradiction – he had an excellent sense of humour that included wearing unusual headgear – and he adjusted to and participated fully in the laboratory's activities, scientific and social. He was fully involved in the life of the laboratory until 1997 and our personal collaboration on science, scientific policy in Portugal and the development of his department continued until his untimely death. He brought the skills of an excellent surgeon and inquisitiveness of a systems physiologist to bear on his research and developed enduring collaborations and friendships with many in the laboratory – Julian Paton (now in Bristol), Ged Goldsmith (now in Southampton) and particularly with Stefan Dawid-Milner (Malaga) whose involvement in the laboratory coincided with Luis'. They maintained an active and increasing collaboration that ensured an Iberian involvement in autonomic neuroscience. Luis' student and subsequent colleague, Isabel Rocha, was strongly involved in that collaboration and hopefully will maintain this into the future.

Luis collaborated on studies involving cerebellar and hypothalamic control of cardio-respiratory function in London, and developed many of these independently in Lisbon. He also established a major clinical autonomic research programme that has grown to be recognised beyond Portugal as significant. He participated fully in the European Clinical Autonomic Society, and was also active in association with colleagues in South America, particularly Chile.

Luis was both religious and politically conservative, a strong monarchist, but socially liberal. He had a strong desire to enhance science and medical education in Portugal and a deep conviction in the importance of physiology. He was an inspirational teacher and had a true commitment to undergraduate medical education. He was a bon-viveur – he enjoyed good food, but not vegetables, and wine and was an amazing and generous host. Together with Ana he had restored a family house in the north of Portugal on the far north-east of the Douro. He liked nothing more than entertaining his English colleagues to the wonders of Portugese wine, both port but also some truly unique table wines. He developed irrigation systems for his vines and olives based on 'physiological principles' developed from his cardiovascular studies. Their intermittent – some would say regular – failures were opportunities for humour and complaints about the backwardness of Portugese labour.

Luis' family had strong medical connections. His father trained as a cardiologist and was Head of the Department of Physiology, University of Lisbon. Following the completion of his MD in Coimbra in 1977, Luis joined his father's department and embarked on studies on arterial chemoreception that resulted in a PhD in 1984. He continued these studies and others on autonomic function until 1998 when he succeeded his father to the Headship of the Department of Physiology. He also shared his father's skill as a pianist, and for many of his friends, it was an occasion in Aberdeen at the time of a Physiological Society meeting that will remain in our memories – coming down to breakfast in the hotel after a vibrant evening to hear Luis playing Chopin. Luis became a Foreign Member of The Society in 1989, and in due course an Ordinary Member. He was a regular attender at meetings. He also used the services of The Society, and the Research Defence Society, in countering growing anti-vivisection tendencies in Portugal. He was fully committed to systems physiology but was instrumental in the formation of the Institute of Molecular Medicine in the Faculty of Medicine in Lisbon leading its Unit of Autonomic Neuroscience. From 1995 to 1998 he served as the Vice-Rector of the University of Lisbon.

It was my honour to be a mentor, colleague and friend of Luis. Our families developed a strong and I hope enduring relationship. His contributions were many and certainly the Medical Faculty in Lisbon is the poorer with his death. His loss is a severe and continuing blow to his parents, and his wife and sons. They do, however, have enormous pride in his contributions to physiology and medical sciences in Portugal.

Mike Spyer

Philip Poole-Wilson

1943–2009

Philip Poole-Wilson was born in London in 1943 and went to school at Marlborough College where he was a very good all-rounder, excelling at games, notably rugby and cricket, and ultimately winning a major scholarship to Trinity College Cambridge to read natural sciences – physics, maths and physiology. Philip enjoyed Cambridge greatly and it was while studying physiology, supervised at times by Alan Hodgkin, that he realised he was more passionately interested in medicine. He modestly remarked 'I decided a career in pure physiology might be difficult and switched to medicine.' He graduated from Cambridge and moved to St Thomas' Hospital Medical School where, in 1967, he qualified in medicine. After several junior posts at the Brompton and Hammersmith Hospitals, Philip returned to St Thomas' joining the academic department of medicine.

His early research interests at St Thomas' Hospital were based on ion movements across heart cells and how these influenced contraction. In 1973 he was awarded a British–American Travelling Research Fellowship from the British Heart Foundation (BHF) and he joined the well-known 'Heart Lab' at UCLA in California under the chairmanship of Glenn Langer. Here he learnt to measure the movement of K^+, Na^+ and Ca^{2+} in the isolated but arterially perfused interventricular septum of the rabbit – a preparation that could be made truly ischaemic. He studied the effects of acidosis and ischaemia on myocardial function and Ca^{2+} exchange and his early results suggested that developed force and Ca^{2+} exchange were more responsive to acidosis within the cell than to extracellular acidosis – something we are much more aware of today.

He brought these techniques back to the UK and in 1976 was appointed Senior Lecturer at the Cardiothoracic Institute under Peter Harris for whom he had eternal regard. His honorary consultant physician status at the National Heart Hospital allowed him to investigate K^+ loss from hypoxia and ischaemic tissue both in the laboratory and in the catheter lab where he was one of the first to measure K^+ and pH in the coronary effluent of humans using catheter-based ion-sensitive electrodes.

In 1980 he was made Reader and in 1982 given a chair by London University. In 1988 he became the Simon Marks and BHF Professor of Cardiology at the National Heart and Lung Institute, at Imperial College. After serving the European Society of Cardiology (ESC) as a councillor in 1988 and as secretary in 1990, Philip became president from 1994 to 1996 and during that time the ESC underwent significant enlargement and reorganisation. From 2003 to 2005 he was president of the World Heart Federation and since then championed the view that degenerative heart disease in developing countries is as important a health problem as infectious diseases. He received many honours, had an impressive publication list, was chairman or co-chairman of many clinical trials and medical committees but looked upon cardiology as 'my hobby'. It was an extremely successful hobby.

In October 2008, following his official retirement, he was made Emeritus Professor and Senior Research Investigator. He was still working and had a diary full of lectures and meetings worldwide. On the day he died he was to have lectured to the medical students in the session just before me but sadly did not turn up. He had collapsed on the train to work from a heart attack – the ultimate irony given his specialty. It was a great pity his well-deserved retirement was cut short by about 10–15 years.

Philip had a wonderful mix of skills. He had a schoolboy fascination for the way things worked and constantly wanted to know more; he loved debate and always had intelligent and convincing points of view. He was always fair, taking on board rational arguments and being prepared to acknowledge the opposing view. He had charm and an engaging sense of fun and optimism. On the one hand he would give considered advice but on the other, had a deep regard for his superiors. He had a continuous and fervent desire to encourage and support young scientists and clinicians and a passion for scientific excellence and being informed. At times he was also quite thick skinned and could shrug off seemingly awkward or discourteous

After a football match during an International Society for Heart Research meeting in Italy. PPW is on the left, Peter Harris (kneeling with ball), Chris Fry (posing while kneeling on the right). Do you know any of the others?

PPW on the day of his 65th birthday. Left to right: Alex Lyon (clinical research fellow), PPW, Ken MacLeod (seated), Sian Harding (standing), Alan Williams and Nick Severs (kneeling).

remarks with aplomb. His good nature, dedication to work and boyish enthusiasm influenced us all.

For me there were two parallel but closely related areas that came together and shaped his very productive life. Following his early interest in the movement of K^+, Na^+ and Ca^{2+} across cardiac cell membranes and how these altered contraction, he became interested in studying similar processes that lead to the decline of contractile function as the heart started to fail. In parallel, his clinical work with George Sutton at Hillingdon Hospital produced a letter in *BMJ* that highlighted a concern with the prevalence of heart failure in the community. Philip brought these two parallel strands together – the pathophysiology and the clinical situation – and helped form and then lead a department that worked at the interface of those disciplines. The process led to him becoming an expert in the manifestations of heart failure at the cellular, organ and whole body levels, an expert in designing therapies appropriate for dealing with the symptoms of the disease and an expert in the disease implications for healthcare worldwide.

Philip's love of science gave rise to many amusing incidents. Here is just one of many anecdotes. I inherited one or two items of equipment from Philip when I joined the department. The results of his fascination for fiddling and tinkering were stored in a locked metal cabinet and with typical gusto and enthusiasm he would open the sacred vault and lend me a small amplifier or gizmo he had made several years previously with rather less focus on electrical safety schemes than would be tolerated today. I have to admit to always being sceptical of their robustness since I nearly electrocuted myself several times on a variety of his home-made devices. He had a habit of earthing the casing (usually a tobacco or biscuit tin) by strategically placing the earth wire stripped of its insulation so that, if the casing was orientated in the way he imagined, it would dangle so as to make contact with any metal surface within the tin. This also meant that, if the item was not orientated exactly as he had envisaged during use, the earth could contact any live wires also strategically placed. I will miss him.

Professor Philip A Poole-Wilson, MA, MD, FRCP, FESC, FACC, FMed Sci, Emeritus Professor of Cardiology, Imperial College, London. Born London 26 April 1943; married 1969 Mary Tattersall (two sons, one daughter); died 4 March 2009.

Ken MacLeod

Alan Williams writes:

Philip and I met in 1976 when (within a couple of months of each other) we joined the Department of Cardiac Medicine of the Cardiothoracic Institute that was based in and around the National Heart Hospital in Marylebone. Philip was a clinical Senior Lecturer and I was fresh from completing my PhD and starting as a post-doc in the group headed by Winifred Nayler. Cardiac Medicine was a small but exciting place to work. Peter Harris, the first professor funded by the BHF, had brought together an unlikely combination of clinical cardiologists, pharmacologists, biochemists and physiologists to investigate the mechanisms underlying cardiac muscle function and how these are altered in disease. My first memory of Philip is of him bounding into the lab (probably singing a snippet of his current favourite aria) and quizzing me on my views on the role of mitochondria in the regulation of cytosolic calcium. This first encounter proved to be typical of our relationship over the next 30-plus years, during which he remained a valued colleague and friend. Philip had enormous enthusiasm and an insatiable desire to understand how things worked. He needed no prompting to enter a debate on any topic ranging from the growing significance of cardiovascular disease in the developing world, to how an ion channel discriminates between calcium and sodium, or the likelihood of Manchester United (his team) winning the Premier League.

Philip will be remembered by many as an outstanding academic clinician and a tireless international ambassador for cardiology. Those of us who worked closely with him in the Cardiothoracic Institute, and its later incarnations, will remember him as a relentlessly cheerful, optimistic (sometimes a bit over optimistic), caring person who thoroughly enjoyed all aspects of his hectic life and displayed an amazing ability to see the good in people. Despite his increasing involvement in multinational clinical trials and the politics of cardiology, he retained his youthful enthusiasm for science and he fought hard to ensure that the contribution made by laboratory science to advances in cardiology should receive appropriate recognition and I will always be grateful to him for that. Philip was the person I turned to when I needed advice on how to

negotiate my way through a difficult administrative issue, whether I should agree to sit on some committee or other, or if I should accept a job offer. I didn't always take his advice but I usually felt much better about life by the time I left his office.

David Eisner adds:

I first met Phillip in 1983 when he invited me to speak at a meeting he was organizing. From our first meeting I was impressed by his charm, wit and warmth. Our paths crossed many times over the next 25 years and I always went away from these meetings feeling happier with the world. His chuckle could make any ridiculous situation seem not so bad. There was never, however, any doubt as to his intellect. He was always an intelligent questioner and would gently, with a characteristic twinkle in his eye, find the weakest part of one's presentation. He was one of the most straightforward and honourable people I have interacted with, qualities that served him well in chairing the Cardiovascular Panel in the 2001 Research Assessment Exercise as well as in his many other organizational roles. Although Phillip had a global reputation as a clinical academic (translational before 'translation' became a cliché), I always got the strong impression that his real love was for what basic science had to offer. With his passing, physiology has lost a strong advocate.

Stuart Cobbe also adds:

I first met Philip when he was a Clinical Lecturer in the Medical Unit at St Thomas' Hospital London, and I was the House Physician. I was struck by his enthusiasm and interest in all aspects of medicine, but particularly in cardiology. Later, he helped to advise me when my career thoughts turned towards cardiology, and I was appointed as a Registrar at the National Heart Hospital. Philip had very recently been appointed Clinical Senior Lecturer, and I had the privilege of being his first Clinical Research Fellow. As many before and after will have experienced, I went from the hectic life of a Cardiology Registrar to the initially lonely experience of being a Research Fellow, responsible for building equipment, developing methods and undertaking research. It was a major culture shock to accommodate, and I will always be grateful to Philip for his never failing enthusiasm and optimism at times when I could not get my experiments to work. With a combination of hard work and good fortune, he helped me to an ultimately successful research project and the award of an MD degree. More importantly, he introduced me to the excitement of basic science and its relevance to clinical cardiology, and this formed the basis of my clinical academic career subsequently in Oxford, Heidelberg and Glasgow. As one of his 'old boys', he never ceased to be interested in my academic activities, and he provided a constant source of sound advice and encouragement. Having known him for nearly 40 years, his death comes as a great shock.

John Ernsting

1928–2009

CB, OBE, BSc, PhD, MBBS, FRCP, FFOM, FRAeS

Air Vice-Marshall Professor John Ernsting, or JE as he was universally known, was an exceptional man and an outstanding human physiologist. His lifelong work on aviation physiology and medicine, the stresses on air crew associated with flying at altitude, and the dangers of decompression led to numerous critical developments of breathing systems and pressure jerkins that had a profound and lasting influence on the design of crew support apparatus worldwide. It also greatly furthered our understanding of the physiology of such extreme environments.

JE was born on 21 April 1928 in Eltham, London, and trained in Physiology and Medicine at Guy's Hospital Medical School, from whence he qualified in 1952. He was subsequently commissioned into the Medical Branch of the RAF, from which he finally retired in 1992 with the rank of Air Vice-Marshall, having been Commandant of the RAF Institute of Aviation Medicine (IAM) at Farnborough from 1988, and previously deputy director of research. From the late 50s he led teams exploring the physiological consequences of loss of cabin pressure or escape from the recently introduced high altitude aircraft. His work was also applied to the design of commercial aircraft such as Concorde, and had a direct influence on the setting of internationally agreed cabin pressures in modern airliners.

On his retirement from the RAF JE came back to King's as a visiting Professor, and continued his research and teaching until his death this year. JE had a passion for education and was an inspirational teacher. He was deeply involved in the creation of the RAF Aviation Medicine Training centre, and subsequently the first postgraduate diploma in aviation medicine, which he later arranged to be taught at King's College London. More recently he developed an MSc in Aviation Medicine, and on his death was working with others

in the department of Physiology at King's to develop an MSc in Space Physiology and Health, the first of its kind in the UK. JE also made invaluable contributions to the teaching of human and applied physiology to both undergraduates and postgraduates, and his enthusiasm and vigour for the subject, unmatched by others a quarter his age, enthused generations of students. He was editor of what is regarded as the key textbook in the field, now known as Ernsting's Aviation Medicine.

JE was a physiologist of the old school, meticulous and thorough, and did not hesitate to act as his own subject under sometimes dangerous conditions. This included decompression to over 100 000 feet, which on one occasion almost led to his death, and use of what can only be described as a neck tourniquet to investigate how long it took to lose consciousness when cerebral perfusion was impeded. He had a strong work ethic, and even in his last days was often in the department shortly after 7am. He was teaching and examining at King's a few days before his death.

He was appointed OBE in 1959 and CB in 1992, and was a Queen's honorary surgeon from 1989 to 1993. He was a past-president of the International Academy of Aviation and Space Medicine, and received the Louis Bauer Award from the Aerospace Medical Association in 2002. Last year a research laboratory in Brazil was named after him. He gave the Halliburton lecture in Physiology at King's in the spring of 2009.

I was privileged to have him in my department, where he was a constant source of enthusiasm and a mine of information, though it was sometimes difficult to keep up with his boundless energy! His death is a major loss not just to King's but also to physiology.

Jeremy Ward

John Coote writes:

John Ernsting's contribution to human applied physiology has largely gone unrecognized by the present generation of physiologists, yet it was immense.

This might have been because much of his research was applied to improving the safety of humans in supersonic flight and the aviation aspects of hypobaric hypoxia. It should not be forgotten that one of his early studies involved the development of a small chamber sealed around the neck to enable increases and decreases in pressure around the carotid sinuses applied to change the activity of the carotid baroreceptors. This was in the mid 1950s and the method is still used to this day and in most recent years has enabled several key questions regarding heart rate and blood pressure control during exercise to be answered. He was an experimentalist of the first order and loved being in the lab.

Council Elections

The following have been elected by Members to serve on *Council* for 4 years with effect from the AGM on 8 July 2009

Stephen Bolsover
Rod Dimaline
Julian Dow
Stuart Egginton
Mary Morrell
Michael Shipston
Andrew Trafford
Michael White

The following have been elected by *Affiliates* to serve as Affiliate Representatives on Council:

Samantha Passey
Federico Formenti

The following are the current *Trustees of the Benevolent Fund*

David Brown (Chair)
Bob Meech
Robert Walker
Thelma Lovick
Rod Dimaline (*ex officio*)
Clive Orchard (*ex officio*)

Adjustment to Membership Subscription fees for 2010

The Society is pleased to announce that those Members who choose to pay their annual subscription by Direct Debit will, from 2010, receive a further reduction to their fees. Furthermore, Undergraduate Members will benefit from the introduction of a one-off payment, which will cover their membership fees for the duration of their undergraduate degree.

Membership category	Membership fees 2010	With DD
Ordinary Member	£90	£70
Affiliate	£20	£15
Associate	£45	£35
School and College Associate	£15	
Undergraduate Associate (join alone)	£15	
Undergraduate Associate (join as group of members)	£10	

Ordinary Members of The Society will continue to be eligible to receive a discount on hard-copy subscriptions to The Society's publications. For 2010, the discount will be 60% of the European retail price, as follows:

The Journal of Physiology: £137

Experimental Physiology: £41

For further information, please contact membership@physoc.org

Cellular & Integrative Neuroscience

Themed Meeting of The Physiological Society, including a focused symposium on:

Sensory processing: From transduction to behaviour

Key Dates

Abstract submission & Registration opens
28 September 2009

Abstract submission closes
19 October 2009

Travel Grant deadline
31 October 2009

Early registration & YPBS deadline
13 November 2009

Sensory processing: Transduction
Gary Lewin (Max-Delbrück Center, Berlin, Germany)
Helen Kennedy (University of Bristol, UK)
Hugh Matthews (University of Cambridge, UK)
Hiroaki Matsunami (Duke University, Durham, USA)

Sensory processing: Subcortical
Maria Fitzgerald (University College London, UK)
Adam Sillito (University College London, UK)
David McAlpine (University College London, UK)

Sensory processing: Cortical
Matteo Carandini (University College London, UK)
Andrew King (University of Oxford, UK)
Irene Tracey (University of Oxford, UK)
Edmund Rolls (Oxford Centre for Computational Neuroscience, UK)

Sensory processing: Central control
Pieter Roelfsema (Netherlands Institute for Neuroscience, Amsterdam, The Netherlands)
Bridget Lumb (University of Bristol, UK)
Mathew Diamond (La Scuola Internazionale Superiore di Studi Avanzati, Trieste, Italy)

Sensory processing: Motor integration and behaviour
Peter Brennan (University of Bristol, UK)
Jens Schouenborg (Lund University, Sweden)
Michael Brecht (Bernstein Center for Computational Neuroscience Berlin, Germany)
Daniel Wolpert (University of Cambridge, UK)

14-16 December 2009
Cardiff University, UK

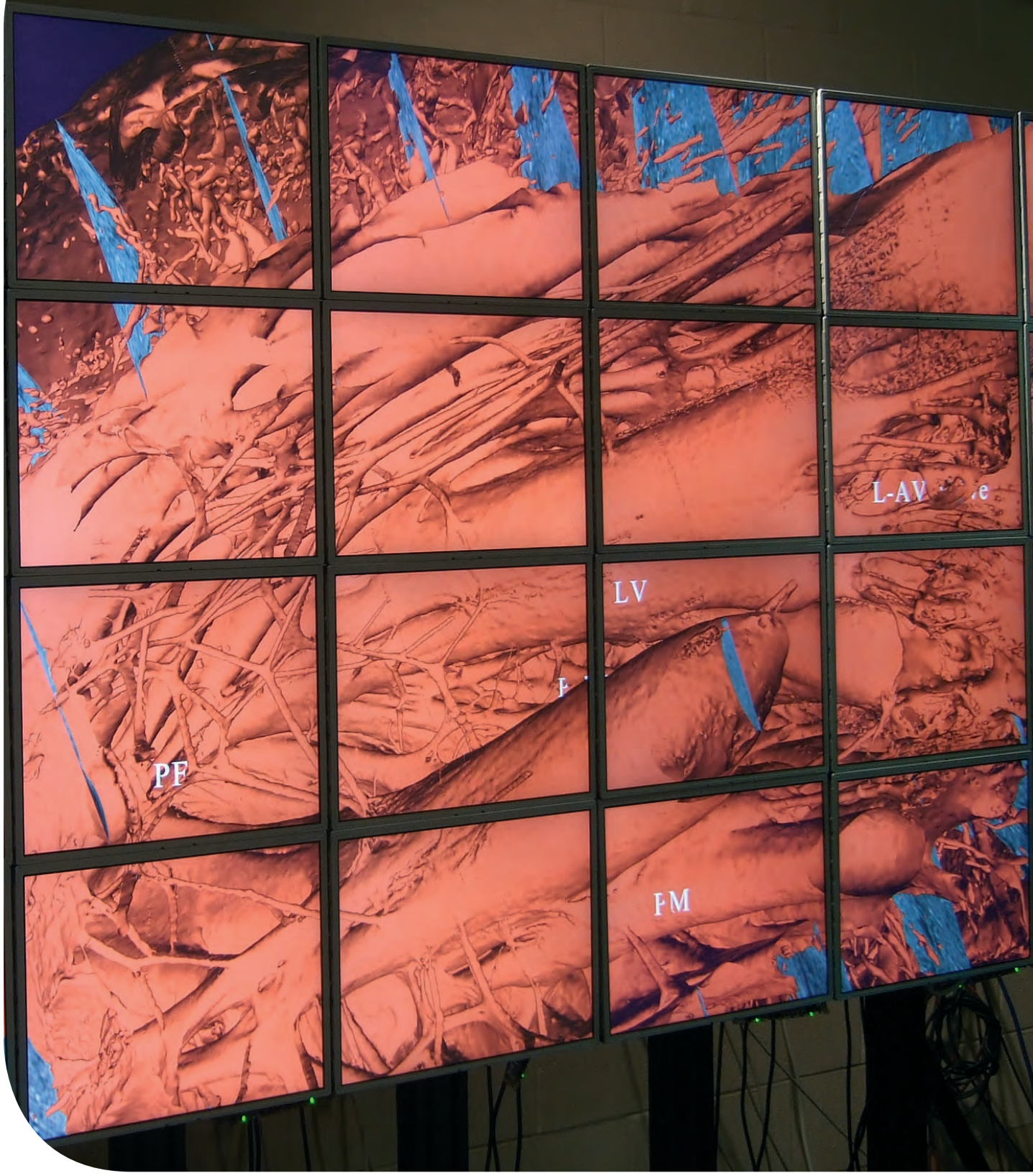
www.physoc.org/cardiff2009

The Bayliss–Starling Prize Lecture was given by Gero Miesenboeck, pictured here with Richard Ribchester (left) and Louise Robson (right).

The Paton Prize Lecture was given by Diethelm Richter (right) pictured with David Paterson.

Physiology 2009 at University College Dublin, 7–10 July

A full report will appear in the next issue of *Physiology News*.



Rabbit whole heart 3D MRI volume, viewed as a long-cut through the left ventricle, with papillary muscles and free-running Purkinje fibres visible (Goodyer *et al*., p. 18).

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