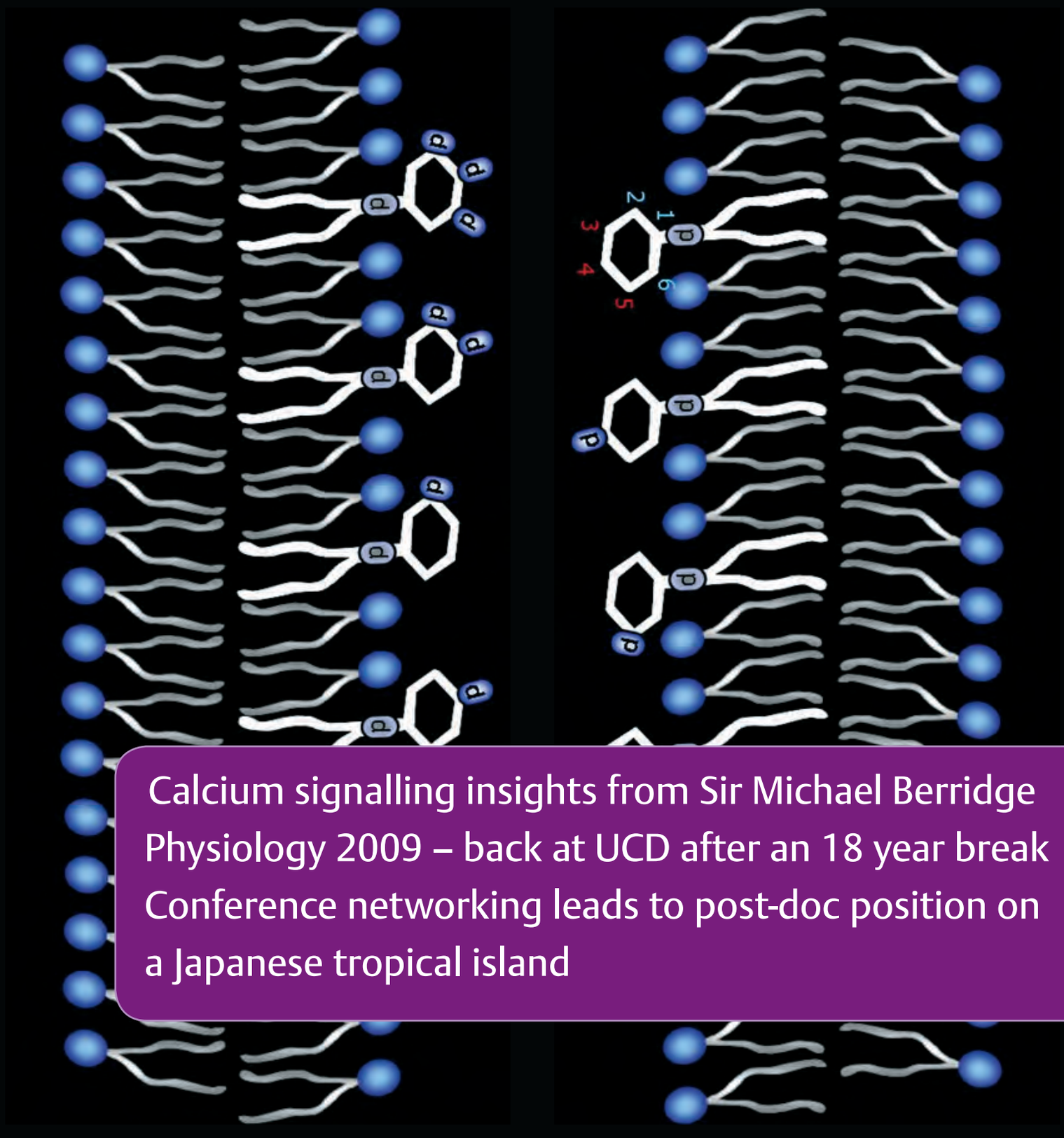
PHYSIOLOGY NEWS

summer 2009 I number 75



Calcium signalling insights from Sir Michael Berridge

Physiology 2009 – back at UCD after an 18 year break

Conference networking leads to post-doc position on a Japanese tropical island

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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'

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Contributions and queries

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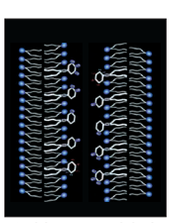
Advancing the science of life



Cover image adapted from a model of membrane inositides (see Interview, p. 34) (with permission of The Babraham Institute: www.babraham.ac.uk/inositide)

PHYSIOLOGY NEWS

PHYSIOLOGY NEWS

Action points

Grants

The Society offers funding through the following grant schemes: Travel Grants, Non-Society Symposia Grants, Outreach Grants, International Teaching and Research Grants and the Vacation Studentship and Departmental Seminar Schemes. For full information, please visit: http://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: http://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 Autumn 2009 issue, No. 76, should reach the Publications Office (magazine@physoc.org) by **9 July 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 Assistant 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 and to reduce the subsequent editing process. The Editorial Board of *Physiology News* tries to ensure that all articles are written in a journalistic style so that they will have an immediate interest value for a wide readership and will be readable and comprehensible to non-experts. Scientific articles should give a good overview of a field rather than focus entirely on the authors' own research.

Format of articles

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

Length of articles

This will be determined by the subject matter and agreed with the Senior Publications Executive.

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 Summer 2009 *Physiology News*

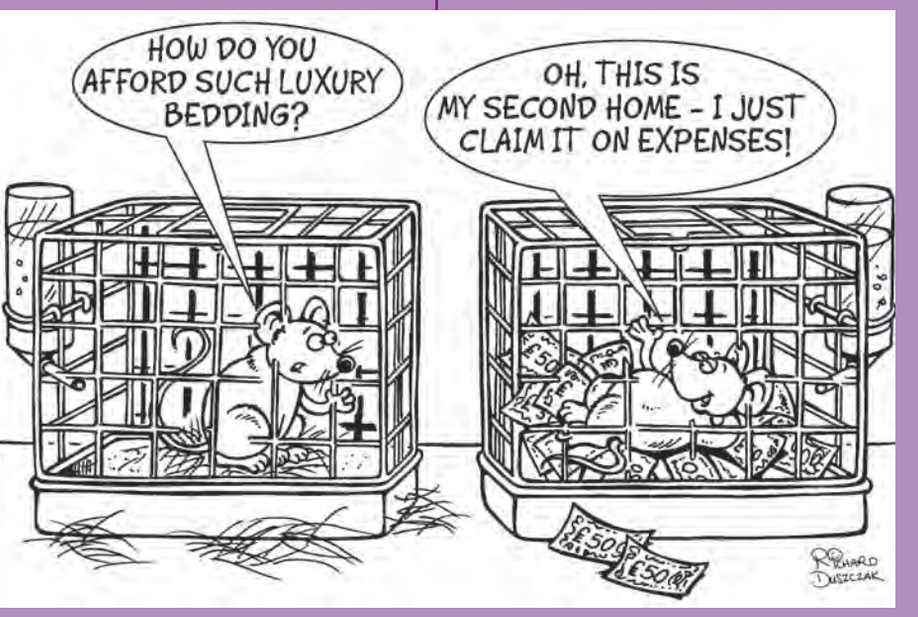
Summer is traditionally conference season, and in keeping with that this Physiology News carries a bumper crop of conference previews and reports (I think I counted 5 of each). I am also pleased to say this is a large issue (64 pages), so it should prove excellent for reading in airports, in train stations, and in idle conference moments – if you have any.

The scientific content includes muscle being stressed and fatigued (pp. 13–16) – I dare say a bit like most of us feel. We also have brains, calcium, being born, growing and sleeping represented in the scientific features – so pretty much all aspects of life are represented in this issue.

Engagement in the broadest sense is likely to prove an increasing part of all our work in the years to come. I am pleased to say we have several features with an engagement or outreach theme (see e.g. pp. 55–58), as well as an editorial asking all physiologists – you – to 'do your bit' for physiology.

And finally, on p. 10 we say our final goodbye to our recently retired Executive Editor, as she looks back over 22 years (sic) with The Society's Publications Office and hands over to her successors, Jill Berriman and Ed Sexton.

Austin Elliott
Editor



A Call to Arms

Earlier this week I went to see a man at University College London (UCL) about a job. He told me he would be in the Medical Sciences building. It didn't ring an immediate bell, so I assumed it would be one of those new blocks springing up on every available spare patch of ground at the UCL main campus. Following the map I found myself, to my slight surprise, walking towards a familiar arch and up the steps that lead to hallowed corridors where the likes of AV Hill, Bernard Katz and Ernest Starling once trod. The plaque read 'Medical Sciences'.

Many readers will already know that the illustrious Department of Physiology that once housed Starling, Katz, and Hill has been merged with neuroscience and pharmacology. Search 'UCL physiology' in Google, click on the top link and an ominous message states "The Physiology website is no longer available... for information on programmes, staff and research in what was Department of Physiology, please use the following links..." Even the old slate "Medical Sciences" sign has been replaced with one bearing the corporate logo, which David Colquhoun amusingly describes on his blog as 'a bilious orange colour' [1]. Is all this juggling of names and "brands" really how it has to be?

Earlier this week, while reading through *Nature*, I was struck by the number of times 'physiology' cropped up – I am rather attuned to the word as I regard it as somewhat of an endangered species. This prompted me to conduct a Web of Knowledge (WoK) search of Nature over the past 5 years using the terms indicated in the first column of Table 1, together with their adjectival derivatives (e.g. physiology, physiological, and not to exclude our American cousins, physiologic). Somewhat surprisingly, 'physiology' did exceedingly well, pretty much head to head with chemistry, another discipline some claim is threatened with extinction. I was amused to note that 'systems biology' – which I recently heard someone call 'physiology with more money' – did rather poorly for an up-and-coming contender.

It could be argued that the word 'physiology' is used more generically than the other terms – but note that it pipped even 'molecular', which one might expect to receive a huge number of generic hits. Whatever the reason for its popularity, it is very good news that people are using the word physiology. The word is alive; it has a pulse – and thus there is hope. My previous state of gloom is reversed.

On some further thought, I realised that I, myself, am guilty of contributing to the demise of physiology – because I gave up responding 'I'm a physiologist' to the question 'What do you do?' I grew fed up with explaining that it is not the same thing as physiotherapy, and changed my answer to 'I'm a scientist'. This is a mistake, because it is a missed opportunity. Every time I say 'I'm a physiologist' I can seize the chance to explain what physiology is. I can, to use an abused phrase, raise awareness. Yes, physiology departments have all but disappeared – but every time we fail to use the word, to write it, to explain it, we hammer another nail into the coffin. So this is a clarion call to "...take arms against a sea of troubles". We are The Physiological Society. We are the foot soldiers of physiology, and if we do not fight, the battle is certainly lost.

So, write the word 'physiology' in every manuscript, grant proposal, and lecture note. Use the word in every talk and lecture that you give. Say 'I'm a physiologist' and explain what it means. Exploit every opportunity. Spread the word. Get sixth-formers thinking about physiology as a degree – to keep the subject viable, we need to create a demand, especially from the next generation. The Physiological Society is implementing initiatives to get the ball rolling, news of which will appear in forthcoming issues of *Physiology News*. But meaningful action comes from individuals – from all of you.

We need to keep as our motto The Society's charitable object 'To promote physiology'. Physiology is a distinguished scientific discipline, with an amazing history and a prosperous future. It is worth saving.

We already have a pretty good 'citation' record in *Nature*. The rest is up to us.

Patricia de Winter

[1] http://www.dcscience.net/?page_id=237

Table 1. PubMed hits in Nature from June 2004 to May 14, 2009 for major traditional scientific disciplines and other biology-related disciplines, plus the word 'molecular'

Search term	PubMed hits
Biology	770 (923)
Chemistry	1639 (380)
Physics	346 (236)
Biochemistry	56 (142)
Medicine	122 (101)
Molecular biology	212
Pharmacology	516 (31)
Physiology	**1706 (272)**
Systems biology	57
'Molecular'	1337

Numbers in parentheses are hits for adjectival derivatives of the main search term and include both British and American usage (see text for example). I selected Web of Knowledge because the searches in both PubMed and *Nature* itself produced inconsistent results. Furthermore, the other database searches seemed to pick up names of journals in the reference list or affiliations, which are specifically excluded by WoK. The results reported here include editorials as well as original articles.

36th IUPS International Congress, 2009

Jul 27–Aug 1, Kyoto, Japan
Function of life: elements and integration

The meeting

On behalf of the organizing committee, it is my great pleasure and honour to extend this invitation to take part in the coming XXXVIth Congress of the International Union of Physiological Sciences (IUPS), to be held in Kyoto, Japan, from July 27 to August 1, 2009 at the Kyoto International Conference Center.

We believe we are now in the midst of developments leading to a new era in physiological research, fueled by the recent revolutionary progress in the biological sciences. We have witnessed the sequencing of the human genome, dramatic progress in computer technology and bioinformatics, and the determination of the structures of a variety of proteins including membrane receptors and channels. The congress will provide an excellent opportunity to review these rapid advances. Many distinguished speakers from all parts of the world will be invited to bring us all up to date on recent developments, both in basic and clinical research, through 29 Invited Lectures (7 Named Lectures, 17 Special Lectures and 5 PSJ Named Lectures), and a wide variety of symposia (57 regular symposia,17 whole-day symposia and 7 PSJ symposia) which cover almost all academic fields related to the physiological sciences.

On top of these oral sessions, we will also have more than 2500 poster

Yasushi Miyashita.

presentations at which participants can discuss their scientific interests with colleagues from many different countries. The total sum of the abstracts of the congress will be more than 3000.

To facilitate participation from all over the world, we supported 150 young researchers by our Travel Grants.

We are ready to invite you to the Congress under the title of "*Function of Life: Elements and Integration*."

Information technology has increased the volume and speed of information flow astronomically. However, it is still no substitute for face-to-face communication. We hope you will be able to join us to share in the exciting scientific dialogue and enjoyable social exchange that will take place in Kyoto.

Yasushi Miyashita
President, 36th IUPS International Congress, 2009
Department of Physiology, The University of Tokyo, School of Medicine

For further information please visit www.iups2009.com

The city of Kyoto

It may be needless to say that Kyoto is a beautiful and historic city where many foreign tourists visit the whole year round. It was the capital city of Japan for a long time and continues to attract visitors with its historic places, including well-known temples and shrines. The motif of the logo of the congress (above) is Kinkaku-ji, one of the most famous temples in Japan. Kiyomizu-dera (top left) is a very popular place for tourists, also good for souvenir shopping. Ryoan-ji (left) is famous for its beautiful Japanese-style gardens paved with cobblestones. Besides the temples, just walking in the city where classic-style houses are preserved will attract you as well. Finally the architecture of the venue (far left) is worth seeing.

Speakers

Named Lectures:
Erwin Neher (Germany)
Akimichi Kaneko (Japan)
Bruce S McEwen (USA)
Sten Grillner (Sweden)
Brian M Barnes (USA)
René Bindels (The Netherlands)
Tobias Wang (Denmark)

Special Lectures:
Frances M Ashcroft (UK)
Stefan Bröer (Australia)
Clara Franzini-Armstrong (USA)
Jeffrey M Friedman (USA)
Yoshinori Fujiyoshi (Japan)
Lily Y Jan (USA)
Kenji Kangawa (Japan)
Ramón Latorre (Chile)
Michel Lazdunski (France)
Atsushi Miyawaki (Japan)
Shigetada Nakanishi (Japan)
Denis Noble (UK)
Fernando Nottebohm (USA)
Mu-Ming Poo (USA)
Nadia Rosenthal (Italy)
Masatoshi Takeichi (Japan)
Joseph S. Takahashi (USA)

PSJ Named Lectures:
Masao Ito (Japan)
Susumu Tonegawa (USA)
Albert J. Hudspeth (USA)
Yoram Rudy (USA)
Osamu Hayaishi (Japan)

Welcome to University College Dublin

We extend a warm welcome to everyone attending the Main Meeting in Dublin, 7–10 July

'*And then I asked him with my eyes to ask again yes and then he asked me would I yes ... and yes I said yes I will yes*'.

Ulysses by James Joyce

And yes the Meetings Secretary said yes; The Physiological Society will return after an absence of 18 years to University College Dublin (UCD), the College that James Joyce attended over a century ago. An issue of fee payment cut short Joyce's interest in medical science and forced him to concentrate on literary pursuits. Physiologists who attended the UCD meeting of 1991 will recall that Physiology at that time was led by Ronan G O'Regan and was a satellite in the city centre, in a building on Earlsfort Terrace in front of that originally designed for the Great Dublin Exhibition of 1865. Paul McLoughlin now holds the Chair of Physiology and in January of 2007 we moved to the main campus at Belfield. Physiology is located within the Health Science Centre and a research institute, named after E J Conway, a physiologist who helped unravel the ionic basis of the resting membrane potential.

Microscope based histology sessions prove riveting for students and staff.

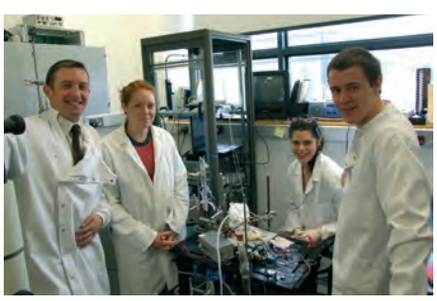
Physiological research at University College Dublin

Translational medicine and animal models of disease

Drs Bund, Jones and O'Halloran employ animal models of disease that link clinical questions to recent advances in physiological science. Current areas of interest include the following common clinical disorders: obstructive sleep apnoea, hypertension and faecal incontinence. We encourage free exchange of ideas, equipment and students; our School of Medicine and Medical Science generously supports the translational medicine PhD programme and associated journal clubs.

The central control of faecal continence

James FX Jones in collaboration with Professors O'Connell (Department of Surgery) and O'Herlihy (Department of Obstetrics and Gynaecology) are investigating the neurophysiological basis for sacral nerve root stimulation in cases of intractable faecal incontinence.



Postgraduate students (from left to right): Colin Peirce, Maria Buffini, Karen Griffin and Ted O'Connor. Karen Griffin is the principal organizer of the Young Physiologists' symposium.

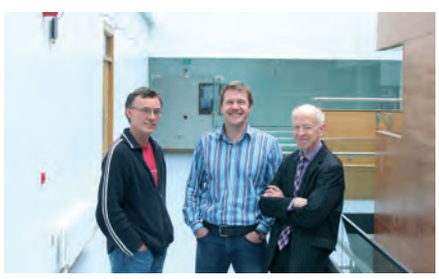
Effects of intermittent hypoxia on control of the upper airway

A team led by Ken O'Halloran is investigating the effects of chronic intermittent hypoxia on respiratory plasticity and function of muscles of the upper airway. Members of the team include Clodagh McMorrow, Jayne Carberry, Richard Skelly, Chrissie Shortt, Deirdre Edge and Ruth O'Connell. Techniques employed include whole body plethysmography, telemetry, force measurement and calcium imaging of isolated muscles.

Postgraduate students (from left to right): Deirdre Edge, Chrissie Shortt and Richard Skelly.

Vascular biology

For most of his career Stuart Bund has been investigating the activity of resistance arteries with particular emphasis on the arterial structure–function relationship in various models of hypertension, particularly the spontaneously hypertensive rat (SHR) model. However, recent years have seen a departure from the systemic arteries to the pulmonary veins and latterly Stuart has nurtured an interest in the contractile function of ureteral smooth muscle.



In the corridors of light (from left to right): James Jones, Ken O'Halloran and John Moynihan.

Chronic hypoxia in the lung

Chair of Physiology, Paul McLoughlin's research group is focused on understanding the key mechanisms in the development and progression of lung disease, in order to identify and validate novel therapeutic strategies. His group is particularly interested in the molecular mechanisms of chronic hypoxia in the lung and the associated alterations to vascular structure. His team includes Christine Costello (senior scientist), Pamela Donohue and Michelle Sands (post doctoral researchers), Brian McCullagh (MD), PhD students Edwina Cahill and Mark Banahan, Susan Harkin (MSc) and Sagarika Hewage (research assistant).

Continuing on the theme of hypoxic lung disease, Katherine Howell, with her PhD student Elaine Colfer,

Paul McLoughlin (extreme left) and researchers at the Conway Institute.

is interested in elucidating the role of vascular growth factors in the co-ordinated maintenance of lung structure *in vivo*. Her research aims to further our understanding of mechanisms involved in the pathogenesis of chronic lung diseases such as emphysema.

Inflammatory lung diseases

John Baugh's research group is interested in the mechanisms in the onset and progression of aberrant tissue remodelling in inflammatory lung diseases. In particular his research is specifically aimed at elucidating the mechanisms that control fibroblast activation, proliferation and differentiation in patients with idiopathic pulmonary fibrosis. His group includes Lili Li, Chris Watson and Patrick Collier and PhD/MSc students Mickael Dubourd, Claire Robinson, Nadia Glezeva, Maojia Xu and Eilika Wulfing.

Transcriptional regulators of hypoxia

Cormac Taylor's group research is directed towards expanding our understanding of the mechanisms by which hypoxia regulates the transcriptional events in epithelial cells. His group is specifically interested in the regulation of global gene expression in response to hypoxia and the modification of transcriptional regulators which underlies the induction of such events, particularly in the setting of inflammatory bowel disease. Cormac Taylor's group includes Eoin Cummins and Terence Agbor (post doctoral researchers), PhD students Kathryn Oliver, Murtaza Tambulwala, John Garvey, Carsten Scholz, Ulrike Bruning, Bettina Schaible and MD student Colin Lenihan.

Cyclic nucleotides in the cardiovascular system

Albert Smolenski is studying the basic mechanisms and protective functions of the cyclic nucleotide signalling network in the cardiovascular system. His group focuses on the identification and characterisation of new protein components involved in cAMP and cGMP signalling, to identify new targets for anti-thrombotic therapy. His team includes Kristina Gegenbauer and Sandra Biewers.

We look forward to welcoming you to Dublin in the summer of 2009.

Katherine Howell
James Jones
University College Dublin

YPS at Dublin

On Tuesday 7 July, Dublin will also play host to a Young Physiologists' Symposium, organised by a group of local, early-career physiologists. The meeting, entitled '*Muscle physiology: function and dysfunction*', will include a morning session on 'Skeletal muscle in health and disease' and an afternoon session on 'Physiological control of smooth muscle'.

These symposia provide an excellent opportunity for physiologists at the early stage of their career to come together and share ideas in a less daunting environment. The Society encourages individuals attending and/or presenting at the YPS in Dublin to register for the main meeting.

Information about the symposium is available on the website: www.ucd.ie/yps2009
If you would like any further information, please email yps@ucd.ie

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

Abstract submission deadline: 29 May 2009

Early bird registration deadline: 31 July 2009

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)

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.

Travel grants (£100 maximum) are available to student members of both the BPS and The Physiological Society to attend this conference.

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

Physiological signalling: from genes to function

On 6 and 7 April 2009, a group of early-career physiologists at The University of Sheffield brought together months of preparation to deliver a Young Physiologists' Symposium, *Physiological signalling: from genes to function*, where the focus was on encouraging multidisciplinary approaches in physiological research.

The first day started with five presentations each from cardiovascular physiology and metabolism and endocrinology. After lunch, we received an inspiring presentation from Frances Ashcroft, entitled '*ATP-sensitive potassium channels: from molecule to malady*'. The presentation followed some of Prof. Ashcroft's scientific discoveries, teaching the audience many lessons about the difficulties of science.

In the afternoon, about 35 delegates attended careers sessions in either Fellowship and Grant Writing or Communicating Science. Both sessions were very well received and generated interesting feedback and questions.

In the evening, the conference relocated to the Winter Gardens in the centre of Sheffield. The Winter Gardens house 2500 plants from around the world, covering 70 m in length and 22 m in height. This impressive display provided the backdrop for 30 scientific posters from the four themes of the symposium: Cardiovascular Physiology, Metabolism and Endocrinology, Non-Excitable Cell Signalling and Neuronal and Sensory Physiology. Everyone really seemed to enjoy the venue and dinner, which prompted lots of discussion late into the night!

The following day included five presentations each from Non-Excitable Cell Signalling and Neuronal and Sensory Physiology. After morning coffee, sponsored by Cairn research, Mark W Hankins delivered a motivational

Evening in The Winter Garden (top) and the organising committee (below).

presentation entitled '*Melanopsin: a new light in the eye – from gene to function and behaviour*'. This was a demonstration of a truly multidisciplinary research effort, which spanned microarray genetic screens through to physiology characterisation and circadian entrainment.

The standard of YPS presentations was outstanding in science and delivery, creating a monumental task for our judges (Frances Ashcroft, Mark Hankins, Matthew Holley, Wen Jiang and Trevor Wardill). Prizes were awarded for the best oral presentation (Hannah Boycott, *Inhibition of T-type calcium channels by carbon monoxide*), the best poster (Moji Musa, *Substance P regulation of mouse cremaster muscle microvascular permeability*) and the students' favourite presentation (Dayne Beccano-Kelly, *Voltage gated potassium channel Kv4.3 is modulated by hypoxia and the AD related peptide Aβ in rat and human tissue*). These excellent presentations evoked lots of questions and discussion from the audience and judges.

I would like to thank all the organising committee for their tremendous efforts and all the other people from the Department of Biomedical Science that helped make the event extremely memorable and rewarding for all.

This event would not have been possible without the generous funding from The Physiological Society, The Genetics Society, The Department of Biomedical Science and our commercial sponsors (Nanion, Cairn Research, VWR, Olympus, Qiagen and Newport).

Trevor Wardill
Juusola Lab, Department of Biomedical Science, University of Sheffield
(on behalf of the Young Physiologists' Symposium organising committee).

If you are interested in organising a Young Physiologists' Symposium at your university, please contact education@physoc.org

PHysiologists' Image Library & TEaching Resource

The Society is developing **Philter**, a new, high quality web-based resource to help Members illustrate and enliven lectures and seminars, and to give access to teaching software. It will offer teachers and researchers an attractive platform to showcase their work: acceptance for Philter will become an acknowledged mark of quality.

Contributions are sought in most formats (including JPG, PowerPoint, PDF, MS Word and .exe (PC) or Mac-compatible self-contained programs). Anything from single images to full PowerPoint lectures can be considered. Programs simulating and demonstrating physiology are welcome, as are movies of 'classic' or the very latest experiments. Once Philter is fully implemented, submission will be possible online.

Philter will reside on The Society's website, with some items 'Members only', and others more tightly restricted (e.g. items featuring explicit animal work). There will be links to related resources, a discussion forum and, we hope, a Wikipedia-like feature.

Submissions or enquiries should be emailed to cstokes@physoc.org

Epithelial form, function and environment

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

Epithelia separate the outside world from a well balanced internal milieu. The barriers are constantly challenged by a myriad of treats and threats – nutrients and information on the one side, pathogens and physical stress on the other. A detailed understanding of the processes that unfold around epithelial membranes is crucial and will ultimately help to prevent and treat disease.

This meeting focuses on three key aspects in epithelial membrane physiology. The first session is dedicated to the question of how barrier function is established, either *de novo* or after an insult, and how it can repair itself. The second session focuses on issues of border control: how selected substances cross the membrane barrier and why others are rejected, and the impact that disease has on this process. The third session highlights the protective functions of the epithelium and how the environment impacts on this property, as for example in the defence against pathogens. These three topics will be presented by world experts in the field and the program will be complemented with oral and poster communications from young scientists. In addition, it is our pleasure to host the Biller Prize lecture. The broad medical and biological relevance of the meeting aims to attract a multidisciplinary audience both from the UK and abroad.

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)

The Epithelial Research Group at Newcastle University has a strong tradition in investigating aspects of membrane transport and epithelial defence, and the group have made a number of seminal contributions to the field. Recently, novel directions such as translational research, epigenetics and novel model systems are also being explored.

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

Andreas Werner
Mike Gray

Bristol II
The paraventricular nucleus in health and disease

Sunday 12 July 2009, 0900–1730. Baker's Hall, Brasserie Blanc, The Friary Building, Cabot Circus, Bristol, UK

Organised by:
Julian Paton (Bristol)
David Murphy (Bristol)
Mike Ludwig (Edinburgh)

Registration is FREE and includes a Raymond Blanc buffet lunch.

More details and information at our website: http://www.bris.ac.uk/clinicalsciencesouth/hwline/symposium/

Bristol II will take place directly after Physiology 2009 (the main meeting of The Physiological Society, in Dublin 6–10 July 2009: www.physiology2009.org).

Sponsored by: The Wellcome Trust, The British Neuroendocrine Society, The Physiological Society, The University of Florida, The Open Neuroendocrinology Journal and the The University of Bristol.

Confirmed speakers
Colin Sumners (Gainsville)
Roger Adan (Utrecht)
Willis Samson (St Louis)
Song Yao (Bristol)
John Russell (Edinburgh)
Charles Bourque (Montreal)
Jaideep Bains (Calgary)
Debora Colombari (Sao Paulo)
Javier Stern (Augusta)
Glenn Toney (San Antonio)
Joseph Francis (Baton Rouge)
Emma Roberts (Bristol)
Giles Yeo (Cambridge)
Scott Young (Bethesda)
William Rostene (Paris)
Charles Hindmarch (Bristol)
Steve Lolait (Bristol)

Discussants
Mohan Raizada (Gainsville); Alastair Ferguson (Kingston); Nina Japundzic-Zigon (Belgrade); Stafford Lightman (Bristol)

The ageing musculo-skeletal system

Human and Exercise Physiology KCL 09 Themed Meeting

As well as Gordon Brown and assorted world leaders, there was another important group of people in London on 1 April: Members, Affiliates and guests of The Physiological Society at the first Human and Exercise Physiology Themed Meeting, held at the Guy's Campus of King's College London. The meeting was organised by Steve Harridge (King's College) and Carolyn Greig (University of Edinburgh) (co-convenors of the Human Physiology SIG group) and Di Newham (King's College).

Tom Kirkwood started the meeting by defining human ageing. He was followed by a further 17 eminent national and international experts, including the Editor-in-Chief elect of *The Journal of Physiology*, Michael Rennie. Topic sessions included mechanisms underlying sarcopenia, metabolism and contractility of aged muscle, ageing bone and tendon, adaptation to exercise and maintenance of physical independence. The multi-disciplinary approach, from cellular and molecular perspectives through to the science behind falls prevention programmes, worked well. Although the focus was on ageing, the meeting attracted presentations on other aspects of human and exercise physiology. The meeting attracted 184 participants with 19 selected oral and 48 poster communications presented during the course of the meeting. The Society's Blue Riband poster prize winners were Thomas Bowen (University of Leeds), Jamie McPhee, (Manchester Metropolitan University) and Daniel Cannon (University of Leeds).

There was ample opportunity for informal discussion and networking. Thanks to the Spring sunshine, the participants were able to do this alfresco between sessions.

The Society's dinner was held on HMS Belfast (see photo above), with the opportunity for a pre-dinner tour of the ship's museum.

Feedback from participants has been excellent and we look forward to

interesting submissions for our next Human and Exercise Themed Meeting which we hope will take place in 2011. We thank everyone who contributed to the success of this event, with special thanks to Fiona Cook (Steve and Di's PA), Clive Daws (Teaching Services Manager at KCL) and of course to The Physiological Society events team.

Carolyn Greig
Steve Harridge
Di Newham

Sam Lucas.

In early April 2009 the western world's attention was focused on London where the leaders of the 20 largest economies had gathered to discuss the global recession. While these leaders were looking at ways to lessen the impact of an acute (one hopes) credit crisis, 'across town' The Physiological Society's Human and Exercise Physiology Themed meeting had gathered at King's College, London, to discuss an issue that will have an impact on all facets of society for a far greater period. The theme of the meeting was the ageing musculoskeletal system and I had travelled from New Zealand to present data about age-related changes in brain blood flow.

The presentations were of a very high quality and ranged from understanding what the ageing process is at the cellular level to the rather grim reality of mortality rate for hip fractured elderly patients (15% in the first year of recovery). A figure that remains etched in my mind is that of life expectancy for people living in the western world plotted against the years spent living without illness, with the latter not increasing at the same rate. Although we may live longer and be able to see our grandchildren grow up, and if we are lucky our great grandchildren, if we want to do more than just watch them from a bed, then the news is not so great. For me this meeting was a step along the way to addressing this widening gap.

While we cannot, and perhaps should not, stop the ageing process, a common theme that emerged from the meeting was the important role that exercise has in slowing the age-related decline in our physiology. This was the silver lining in an otherwise gloomy forecast. Slowing this decline may be an answer to increasing our healthy life expectancy and thus improving the quality of life for the elderly. Data presented during the meeting indicated that resistance and strength training appears more beneficial for some aspects of ageing health (e.g. mobility), while in other aspects aerobic exercise appears more beneficial (e.g. immune function and weight loss). So just like having a healthy balanced diet through life, it would seem that we need to balance our exercise programmes too. Maintaining muscle strength and quality into old age appears very important in delaying dependence and frailty, and aerobic training may help immune function in the aged and help control weight gain. These data are important for all society and although we may not have all the answers to this ageing challenge, there appears to be some positive interventions that we can use to improve our ageing health.

I would like to acknowledge the New Zealand National Heart Foundation, The Physiological Society and the School of Physical Education, University of Otago for their assistance with my travel expenses.

Sam Lucas

Department of Physiology, School of Physical Education, University of Otago, New Zealand

22 years in the life of The Society's Publications Office

Linda Rimmer looks back on changing times ...

It is hard to believe that so much time has passed since I arrived in Cambridge with two toddlers in tow, back in 1986. Since leaving school I had been employed in a string of jobs from the United Nations Association to the weekly newspaper *Hospital Doctor*, via the House of Commons (twice), the World Health Organization in Geneva, the Royal Institute of British Architects, Roger Williams' Liver Unit at King's College Hospital and the *British Journal of Family Planning*, with stops in the USA on the way. Trevor Lamb, then Press Secretary in The Society's Publications Office, felt this prepared me for a role as his part-time Editorial Assistant, but I doubt he expected me to be here almost 23 years later, albeit in another guise.

From left to right: Jill Berriman, Linda Rimmer and Ed Sexton.

Things were very different back then – submitted (paper) manuscripts were entered manually in a large day book, mailed to outlying Distribution Offices for review and then returned to us by mail for typesetting by Cambridge University Press or rejection. But Trevor was soon dragging us kicking and screaming into the newly developing technological age, installing a computer in our office and setting up the first of several manuscript databases. When I was able to work longer hours, I took on *The Journal of Physiology*'s Editorial Board, Executive Committee and Officers (can I really have seen eight Editors-in-Chief come and seven go?), organising symposia, handling budgets, working with The Society's Publications and Publication Ethics Committees, producing Society Grey Books and Meeting Programmes and, last but far from least, bringing production of The Society's magazine, *Physiology News*, in-house.

I have seen *The Journal*'s Editorial Board change from predominantly UK-based to mostly international membership and their meetings go from a leisurely couple of hours on a Saturday afternoon in London (with wonderful picnic baskets of homemade lunch provided by Barbara Fulton) to regular 2-day marathons in the US; backlogs of manuscripts come and go; authors names in alphabetical order, and not; a change of publishers after 125 years (accompanied by an office move); the Publications Office staff go from 5 to 20 and back to the current 10; the arrival of Richard Dyer's Biosciences Federation in our office (which certainly livens us up when the corks are popping and the paella pan is fired up) – all against the backdrop of the ever-changing format, content, rebranding and publishing procedures of *The Journal of Physiology* and *Physiology News*.

However, now that the long-since ex-toddlers have made their own lives – one with Hearing Dogs for Deaf People and the other in music PR – it is time to pursue other interests that have been on hold for far too long. I leave the production side of *Physiology News* in the very capable hands of Jill Berriman (who has been with The Society almost as long as me) and the rest of my work with Ed Sexton (who has been working in *The Journal of Physiology*'s Distribution Office since May 2008).

It has been a pleasure to know so many of you through my various roles in The Society – I wish you all a fond farewell.

Linda Rimmer

... and Jill Berriman reflects on the production of her first issue of *Physiology News*

Like Linda, I also have been with the Society for many years (since 1991) and have gone from role to role – first as Copy Editor and Proof Reader within the Cambridge University Press building, to Senior, then Chief Production Editor, before progressing to Managing Editor. I remember my husband John telling me when I first applied for the job that I would be much too bored after a few months – but that was assuming that things never change. They do and often. I gave up that post when, in 2004, my husband and I decided to change our lives completely by moving to the 'Big Apple'. With problems like work visas, I continued with The Society as a Production Editor working from home, but with home just a bit further from the office than for 'normal' home workers. We had a fantastic couple of years in New York, but eventually decided to return to the UK, where I settled back into *The Journal of Physiology*, plus work on meetings abstracts. It wasn't until the imminent departure of Linda, when The Society were looking for someone else to take over the production of *Physiology News*, that I thought that this might be a great opportunity to get involved in a different side of The Society.

I was used to journal work being very predictable – you get your manuscripts and figures and these fit into a regular template. You never have to worry where the next paper is coming from – there are *always* papers to be done. The magazine is a different kettle of fish – never knowing quite which articles will be submitted, how they will go together, and the possibility of someone deciding not to write an article at the last minute etc. (mentioning no names, of course).

Linda and I had discussed all the magazine work carefully and she had pointed out the need to work within the budget, so I was a little perturbed to find, once all the articles were in for PN74, that my target of 52 pages had been totally lost. It seemed as though it was going to be a bumper issue – 64 pages. Too late to change, we proceeded with all the articles but I have been warned – the next issue must be smaller.

It hardly needs saying that Linda will be a hard act to follow. Over the 18 years I have been working with her, she has always impressed me with her calm unflappable thoroughness. I feel honoured to have had her as a coach on *Physiology News*. If I can do as good a job as her, I will be well satisfied.

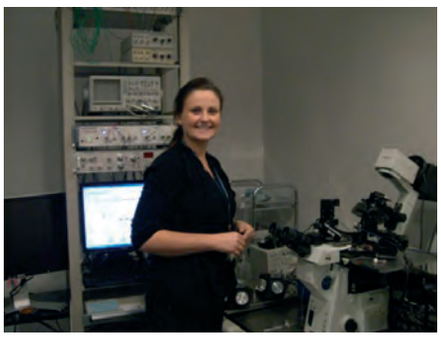
Jill Berriman

Letters from Japan 1 – Conference networking materialises into dream postdoctoral position on sub-tropical island

In January I got on a plane to Okinawa, a sub-tropical island in Japan, to begin a 2 year postdoctoral position. Image search for Okinawa on Google and combine those pictures in your head with a great scientific job and you'll understand my enthusiasm! I'm going to share some of my new experiences in the next issues of *Physiology News*. As young scientists, we all think about moving abroad in our careers and a diary of my experiences may be of interest to people considering taking this direction.

So, first, how did I decide on Japan? At the Federation of European Neurosciences conference in Geneva in July 2008 I overheard a gentleman say, 'so, if you know anyone who is looking for a postdoc on a tropical island let me know', and I thought 'me'. We got chatting, but worked in different areas so didn't really discuss science in detail. In my search for postdoctoral positions online I came across an advert for a postdoctoral electrophysiologist at the Okinawa Institute of Science and Technology in Japan. Although a new brain area to that I worked on for my PhD, the techniques required were the ones I used and the advertiser was the gentleman from the lobby at FENS! So, I applied, mentioning the chat in the lobby at FENS, went for interview and here I am writing this article from my office in Okinawa. Conference networking can have very exciting results – take note!

In the weeks before I left I had the stresses of moving away (a long way) from home. Obviously I was sad to leave my family, friends and pets. I had to rent my house, sell my car and find homes for my horse and two cats. I had to sign a legal document



Fiona and her rig.

to allow my dad to regulate my affairs – luckily my bank account was empty anyway! I did two trips to London to the Japanese Embassy to collect a visa. Because my contract in Japan could not be processed until I had my PhD, organisation for the move remained in the air and then seemed to happen very fast. I got the exact flight times 4 days before I got on the plane and had no idea what I needed to do when I arrived. But the uncertainty and chaos masked the real anxiety about the move.

Fiona and Emma-Karin Millers, a fellow postdoctoral researcher in Okinawa from Sweden sample some local cuisine after a day at the beach.

Upon arrival in Okinawa I was greeted by a driver with a board saying 'Dr Fiona Randall' – then I felt I had made it! Bright and early the next day I was in the lab, familiarising myself with equipment and discussing project plans with my new boss, Gordon Arbuthnott. A thing I never thought of until I came to Japan was the different alphabet – this makes it difficult to even guess what things are. There is a lot of paperwork to be done in Japan for immigration, apartment rental, bank accounts etc. none of which I can read. A trip to the supermarket can take hours as I debate with myself over what things are – sometimes I buy what looks like milk and it is yoghurt. The world outside work is less familiar than the world in the lab, where most equipment, even if labelled in Japanese, looks familiar. It is strangely easier to work out a microscope function here than a bottle of milk. I spent my first few months in a state of, well, excited confusion. I was learning a new brain area and some new techniques and wasn't even competent to buy milk. It was funny most of the time but sometimes I felt I was losing my mind.

Fiona and Marianela Garcia-Munoz check out the new Brain Mechanisms for Behaviour office at the building site for the new laboratories due to open in 2010.

Three months in, I feel that Okinawa is home. I have a great apartment, a convertible car (it is a waste not to when you see the sun so much) and know my way around in the lab. Work is going well and I am presenting my first talk in Dublin at Physiology 2009. The institute here in Okinawa is new and we move to our new laboratories at the end of the year. There is a lot of exciting science happening here and I know that in the future I will look back and feel very proud to have been a part of this new institute. I am taking part in an English club at a local school which gives me chance to spend time with Japanese people and learn more about their culture, as well as tell them about mine. Skype and the internet make it easy to talk to the people I left behind: in fact I probably speak to them more now than I did in the UK. I have also had chance to learn to scuba dive, kickbox and deep-sea fish. I can even say a few words in Japanese.

Fiona Randall

When fatiguing cycling muscles complain, the brain insightfully responds!

When oxygen transport from the lungs to the legs is reduced (e.g. at altitude), the muscles utilized to ride a bicycle (locomotor muscles) fatigue faster and a person's cycling time to exhaustion – against a *fixed* resistance – is significantly shorter compared with sea level. On the other hand, when oxygen transport to the locomotor muscles is increased (e.g. via blood doping or breathing 100% oxygen), the rate of fatigue of the working muscles is a lot slower and the person's time to exhaustion is substantially longer compared with sea level. Interestingly, at exhaustion (subject is not able to continue exercise against the same fixed resistance), whether it is reached during cycling at sea level, or on the top of a 3000 m mountain, or while breathing 100% oxygen, the level of peripheral locomotor muscle fatigue – and the associated intramuscular milieu determining this level – is identical (Hogan *et al.* 1999; Amann *et al.* 2006, 2007)! Also interesting, when the fatigued muscle of a human, who just reached the point where he is unable to voluntarily continue the exercise against a *fixed* resistance (i.e. exhaustion), is artificially innervated – or 'driven' – via transcutaneous electric motor nerve stimulation, the muscle is able to continue the exercise (Löscher *et al.* 1996). These observations suggest that humans stop exercising once a certain level of locomotor muscle fatigue is reached and that, by stopping the exercise at this particular level of peripheral fatigue, a certain degree of muscular functional reserve is preserved.

The situation is somewhat similar with time trial exercise. During a time trial performed on a bicycle ergometer, subjects cover a set distance as fast as possible and are able to adjust power output (i.e. speed) by switching gears – just like on a real bike. We recently observed that during a 5 km cycling time trial performed at simulated altitude (locomotor muscles fatigue faster), central neural drive and consequently power output/speed is down-regulated, whereas during the same time trial performed while breathing 100% oxygen (locomotor muscles fatigue slower), central neural drive and power output/speed is up-regulated compared with sea level. Astonishingly, despite the different performances achieved in these three time trials (fastest with 100% oxygen and slowest at altitude), the magnitude of locomotor muscle fatigue at end-exercise was identical (Amann *et al.* 2006). Considering this, it appears that the down-regulation of central neural drive and power output at altitude ensured that the rate of development of locomotor muscle fatigue was slowed and end-exercise peripheral fatigue prevented from exceeding a certain limit. On the other hand, the up-regulation of central neural drive and power output while breathing 100% oxygen accelerated the rate of development

Markus Amann (left) and Jerome A Dempsey.

of peripheral locomotor muscle fatigue; however, end-exercise locomotor muscle fatigue was still limited to that 'threshold'. It seems like the brain, consciously and/or subconsciously, senses peripheral fatigue and alterations in the associated intramuscular metabolic milieu (and/or it's rate of change) – presumably via the cortical projection of metabosensitive small-diameter muscle afferents (group III/IV) – and regulates central neural drive to restrict the development of locomotor muscle

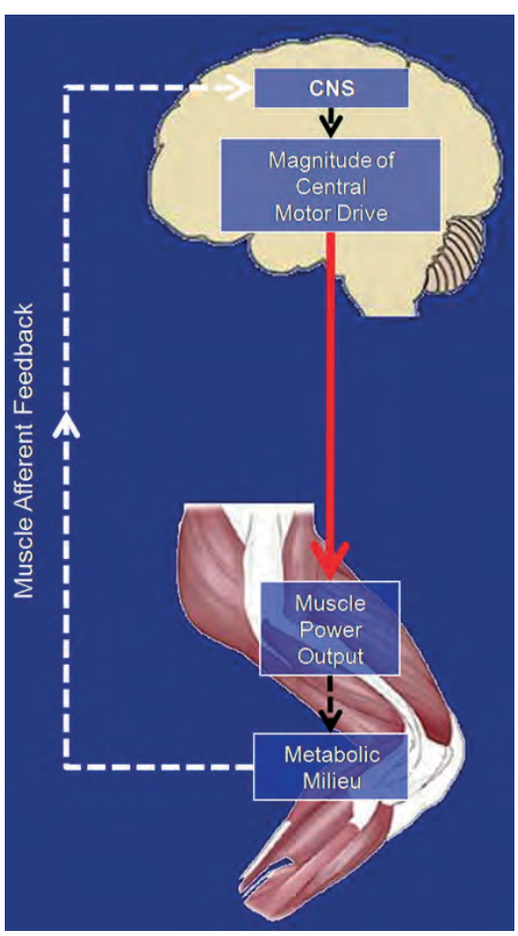


Figure 1. Schematic illustration of our proposed and tested model. The continuous red line indicates efferent nerve activity (central motor drive), the dashed white line indicates afferent nerve activity. This regulatory mechanism shows that the cortical projection of muscle afferents (inhibitory feedback) affects the determination of the magnitude of central motor drive which in turn determines power output of the locomotor muscles. The magnitude of power output determines the metabolic milieu within the working muscles which in turn determines the magnitude of the inhibitory afferent feedback. Based on our data, the purpose of this feedback loop is to limit peripheral locomotor muscle fatigue to an individual threshold which is never exceeded. From Amann & Dempsey (2009).

fatigue to a certain threshold that varies between individuals. Based on these observations, we formulated a hypothesis claiming that locomotor muscle afferent feedback exerts an inhibitory influence on the determination of central motor drive during high-intensity, whole-body endurance exercise and restricts the development of peripheral locomotor muscle fatigue to an individual critical threshold (Fig. 1) (Amann *et al.* 2006).

To experimentally evaluate whether ascending sensory pathways affect the magnitude of central motor drive, we recently blocked locomotor muscle afferents during a 5 km cycling time trial via lumbar epidural anaesthesia (lidocaine). In the absence of neural feedback from the legs, central motor drive was substantially higher compared with the control race performed with an intact regulatory feedback mechanism as illustrated in Fig. 1. However, since local anaesthetics also reduce efferent nerve traffic between the injection site and the end-organ, less 'push' arrived at the locomotor muscles and time trial performance was expectedly reduced (i.e. longer time to finish the race) (Amann *et al.* 2008).

To circumvent this problem and to adequately determine the effect of locomotor muscle afferents on exercise performance and the development of peripheral fatigue, we repeated the study and used placebo *vs* fentanyl, an opioid analgesic, to selectively block the activity in ascending sensory pathways without affecting motor nerve activity (Amann *et al.* 2009). We clearly emphasize that we only blocked opioid-mediated afferents; other ascending pathways were unaffected by this intervention. Similar to the first study, blocking somatosensory feedback from the legs released a centrally mediated 'brake' on central motor drive but this time, exercise performance was substantially improved over the first half of the race. Evidently, the missing neural feedback tricked the athletes to overestimate their work capacity and they 'chose' a power output which exceeded their aerobic capacity and quickly resulted in severe muscle acidosis, leading to a curtailed power output during the second half of the race – *despite continuing high central motor drive*. Although the overall time trial performance was similar between the trials, the induced acidosis in the fentanyl race accelerated the rate of development of locomotor muscle fatigue – but this was, due to the missing neural feedback, 'unseen' by the brain. Therefore, the brain 'allowed' or 'tolerated' the exercise-induced development of locomotor muscle fatigue significantly beyond levels as observed following the placebo race, i.e. with intact neural feedback system. All athletes substantially exceeded their critical threshold which resulted in severely impaired locomotor muscle functions and acute ambulatory problems (Amann *et al.* 2009).

In conclusion, our results suggest that neural feedback from the working and fatiguing muscles exerts inhibitory influences on the determination of the magnitude of central motor drive during high-intensity endurance exercise. Furthermore, it appears that neural influence of exercising muscles on the brain causes a restriction of the exercise-induced development of peripheral muscle fatigue to an individual's critical threshold – presumably to prevent severely impaired muscle functions and to preserve a functional muscle reserve following exhaustion induced via whole-body endurance exercise. Finally, we propose that somatosensory feedback is necessary to match/adjust central motor drive to the metabolic milieu of the working muscles to avoid acidosis and guarantee optimal exercise performance.

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Muscles under stress

It is often assumed that skeletal muscles are not among the targets of the sympathetic nervous system (SNS). However, muscles receive abundant (nor)adrenergic innervation, mostly but not exclusively addressed to arterioles, and are affected by the hormone adrenaline, released by the adrenal medulla (under sympathetic control). In fact, catecholamines modulate many functions of skeletal muscle fibres, ranging from excitability to contractility to metabolism

The first evidence of adrenergic modulation of muscle function dates back to the end of the 19th century, before the biochemical identification of catecholamines. At that time, scientists investigated the function of the adrenal gland by systemic administration of 'suprarenal extracts' in experimental animals. The results were puzzling as the animals exhibited reactions leading to death with different time courses and symptoms, so that the gland was believed to be a poison collector. Oliver & Schäfer (1895) first described specific effects of suprarenal extract on skeletal muscle as well as on the heart and other organs and observed increased amplitude and prolonged duration of the twitch force of the frog gastrocnemius muscle (Fig. 1).

Since then, the issue has been investigated extensively, and catecholamines are now known to modulate several processes in skeletal muscle fibres (Bowman, 1980; Roatta & Passatore, 2008), particularly through β (mainly β_2) adrenergic receptors. Most of these actions are functionally meaningful in the context of a 'fight-or-flight' reaction, i.e. the state of alertness generally provoked by an impending threat or danger. This condition

Silvestro Roatta (left) and Dario Farina.

is characterized by a generalized activation of the sympathetic nervous system (SNS) that is aimed at supporting the intense motor activity necessary to face or to escape from the threat; this occurs in animals as well as humans. Although in the latter the motor component is often suppressed by social constraints, the autonomic activation still occurs under stressful conditions, with several side effects. In addition, it is worth emphasizing that circulating adrenaline (ADR), rather than neurally released noradrenaline, is the main mediator of the sympathetic action on skeletal muscles, given the much higher affinity of ADR for the β_2 adrenergic receptors. This is important from the functional point of view, since there is a different release of the two substances depending on the context and on the stressor. For instance, ADR release is stimulated by painful stimuli and during panic attacks but not by cold exposure.

Catecholamines exert an anti-fatigue action on muscle fibres. By potentiating the action of the Na^+-K^+ pump they help in counteracting the decrease of ionic gradients across the cell membrane that occurs under intense activity and that impairs the excitability of muscle fibres, thus contributing to fatigue.

Moreover, by acting presynaptically at the motor end-plate, catecholamines potentiate the neuromuscular transmission. This action does not have a functional consequence in normal conditions, given the high reliability of the motor end-plate in transmitting excitation to the muscle fibre. However, in conditions in which the fibre excitability is impaired (e.g. during intense muscle activity), this effect may be useful.

Catecholamines increase the availability of energy substrates by promoting glycogenolysis and glucose absorption. β_2 agonists also affect protein metabolism by slowing proteolytic processes and by potentiating protein synthesis. They are indeed employed as anabolic drugs in the livestock industry and in certain power-related sports, e.g. weight lifting and bodybuilding.

Finally, going back to the initial observation of Oliver and Schäfer, catecholamines modulate the contractility of muscle fibres (inotropic effect). In his extensive review, Bowman provided evidence that the adrenergic action depends on the muscle fibre type: the twitch force is increased in amplitude and duration in fast-twitch muscle fibres whereas the opposite effect is exhibited by slow-twitch fibres (Bowman, 1980) (Fig. 2). More recent *in vitro* studies elucidated the mechanisms underlying these effects. The twitch potentiation is

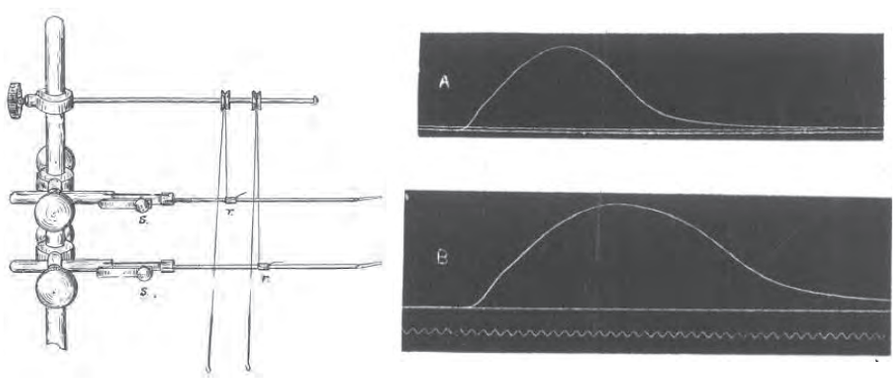

Figure 1. Two figures taken from the original work of Oliver & Schäfer (1895) measuring the effect of ADR injection on different organs. Left panel, diagram of method employed to record the contractions of the parts of the mammalian heart. Right panel, effect of suprarenal extract upon muscle contraction in the frog. *A*, normal muscle-curve of gastrocnemius; *B*, curve taken during suprarenal poisoning, but otherwise under the same conditions as *A*. Time 0.01".

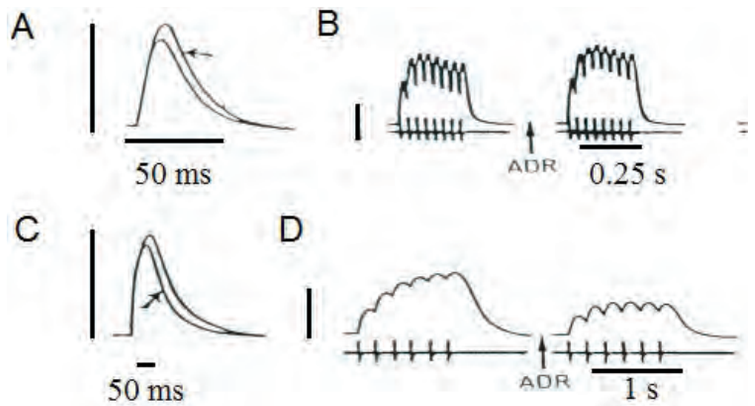

Figure 2. Effect of adrenaline injection (ADR) on single twitch force (*A* and *C*, effect of ADR indicated by the arrow) and on subtetanic electrically elicited contractions (*C* and *D*) of fast-twitch (*A* and *B*) and slow-twitch muscles (*C* and *D*) in anaesthetized animal preparations. In *B* and *D* the vertical marks in the lower trace indicate the electrical stimulation. Vertical calibrations, 5 N. Modified from Bowman (1980).

mediated by enhanced Ca^{2+} release from the sarcoplasmatic reticulum, and this mechanism is shared by both fibre types. The twitch decrease and shortening is instead related to an increased rate of Ca^{2+} re-uptake into the sarcoplasmatic reticulum, an effect mediated by phospholamban, a regulatory protein controlling the activity of Ca^{2+} pumps (Ha *et al*. 1999). In a similar way, catecholamines increase the relaxation rate of the heart (positive lusitropic effect). This effect is not exhibited by fast twitch muscle fibres because they lack phospholamban, whereas it may be responsible for a marked weakening of slow-twitch fibres (Fig. 2*D*), as documented in many animal experiments and *in vitro* studies. We recently investigated whether this phenomenon is functionally relevant by analysing it during voluntary contractions and physiological activation of the SNS in humans (Roatta *et al*. 2008). In this study, healthy men were subjected to the cold pressor test (CPT, a sympathetic activation test based on the painful immersion of a hand in icy water) while the activity of low-threshold (presumably slow-twitch) motor units was recorded from the tibialis anterior muscle during isometric ankle dorsi-flexion. The experiments showed that, as compared to control conditions, the discharge rates of the recruited motor units increased in order to attain the same force level (10% of the maximum voluntary contraction) during CPT (Fig. 3). This observation indicated a weakening effect of SNS activation on the investigated muscle. In addition, the twitches of single motor units, estimated by the spike-triggered averaging technique, exhibited an increased relaxation rate during CPT, confirming the observations in animal experiments. Although these data need to be confirmed and substantiated by other experiments, they indicate that the influence of the SNS on skeletal muscle is not negligible as it can produce appreciable changes in muscle function and motor control.

One may wonder how a 'weakening' effect could fit with the 'fight-or-flight' reaction where more muscle power would be expected. It should be noted, however, that (1) the big, fast-twitch motor units are not affected by this action; and (2) the maximal (tetanic) force of slow-twitch motor units is not impaired by this effect, although a higher discharge rate will be required to attain it.

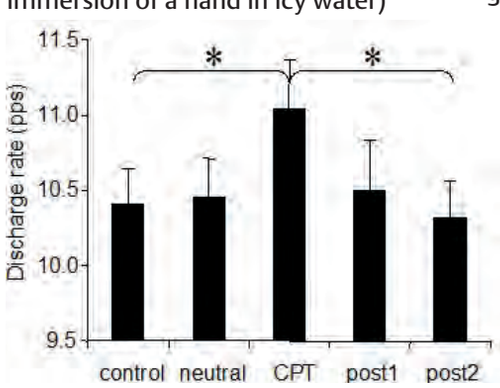

Figure 3. Average discharge rate of tibialis anterior motor units in isometric contraction (10% of maximum voluntary contractions) is increased during hand immersion in icy water (CPT), as compared with the other conditions: no hand immersion (control, post1, post2) and immersion in water at neutral temperature (neutral); $^{*}P < 0.05$. From Roatta *et al*. (2008).

Moreover, a faster relaxation rate of slow muscle fibres may be useful in the fast movements required in the 'flight'. In this respect, it is interesting that chronic administration of β_2 agonists produces a transformation of type-I (slow-twitch) to type-II (fast-twitch) in muscle fibres.

On the other hand, some of these actions may be harmful to the muscles under stress-related adrenergic overload, and it has been hypothesized that they might be implicated in the development of musculoskeletal disorders.

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Novel player in insulin resistance: focal adhesion kinase

Focal adhesion kinase (FAK) has recently been implicated in the regulation of insulin resistance *in vitro*. We hope the results of this study will provide a new strategy for the synthesis of new chemicals for FAK activation and promote development of new drugs against insulin resistance

Development of insulin resistance in the peripheral organs is one of the key defects associated with type 2 diabetes and obesity. However, the precise regulatory mechanisms of insulin resistance is not completely deciphered. Reports suggest cross-talk between focal adhesion kinase (FAK) and insulin signalling. Recent studies have associated FAK with insulin resistance. *In vitro* as well as *in vivo* studies have highlighted the role of FAK as a potential, novel player regulating insulin resistance. These studies have tremendous potential in presenting FAK as a possible drug target and in creating possibilities of new drug development against insulin resistance.

Insulin resistance and search for a novel target(s)

Insulin resistance is a condition in which normal concentrations of insulin produce a subnormal biological response in the primary target tissues such as skeletal muscle and adipose tissue (Taniguchi *et al*. 2006), and exhibit reduced insulin-stimulated glucose uptake and metabolism. Insulin resistance is a defect of insulin signal transduction. A variety of protein kinases and their substrates have been shown to be important regulators of insulin resistance at the molecular level. However, the signalling mechanisms involved remain elusive. Current estimates suggest that there will be over 350 million people worldwide affected by type 2 diabetes by the year 2030 (Turner & Heilbronn, 2008). Thus, considering the explosion of insulin resistance world wide there is an immediate need to explore novel and efficient drug targets.

Focal adhesion kinase (FAK) and insulin signalling

FAK is a non-receptor and non-membrane-associated protein

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tyrosine kinase found at the focal adhesions (Schlaepfer *et al*. 1999). FAK, a highly conserved protein expresses and undertakes a variety of functions in most tissues and cell types. Phosphorylated FAK can bind and integrate with multiple signalling pathways thereby acting as a molecular 'switch' in response to signals from the external environment and regulating various cellular processes (Romer *et al*. 2006).

In 1995, Knight *et al*. reported that insulin causes dephosphorylation of FAK, thus suggesting an antagonistic action of insulin on the integrin signalling. Co-immunoprecipitation of insulin receptor substrate-1 (IRS-1) with $\alpha_v ß_3$ integrin after insulin stimulation indicated a putative co-operation between two signalling proteins (Vuori & Ruoslahti, 1994). Czech and co-workers reported evidence for the crosstalk between integrin and insulin signalling molecules (Guilherme *et al*. 1998). Baron and her group have provided the first evidence demonstrating FAK as a direct substrate of insulin and a direct interplay between FAK and IRS-1; however, no interaction was observed between FAK and the insulin receptor (IR) (Lebrun *et al*. 1998). Further, it was observed that FAK could induce IRS-1 tyrosine phosphorylation resulting in an increased association of IRS-1 with p85α, SHP-2 and Grb 2. Lebrun *et al*. (2000) presented an interesting finding utilizing FAK-knockout fibroblasts where IRS-1 expression was observed to be abolished in FAK-knock out cells. Cheung *et al*. (2000) evaluated the role of FAK in TNF-α-induced insulin-resistant hepatocytes demonstrating that insulin acts as an activator of FAK by increasing its tyrosine phosphorylation. A new dimension was added to FAK functions when Huang *et al*. (2002) reported regulation of glycogen synthesis by FAK expression in hepatic cells. Data showed a direct interaction of FAK with GSK3-ß which made the group conclude that FAK acts downstream to IR, IRS-1 and PI3K via interaction with Akt and GSK3-ß. Recently the research group of Brayer-Ash knocked down FAK expression by 50% and reported impaired insulin-stimulated 2-deoxyglucose (2 DOG) uptake and concluded that the integrin signalling pathway potentially plays an important regulatory role in muscle insulin action (Huang *et al*. 2006). In light of the above findings, it is safe to conclude that FAK has important roles to play in regulating insulin signalling. However, questions regarding the physiological role of FAK in the regulation of insulin signalling, especially under pathophysiological conditions like insulin resistance, remain an enigma.

FAK and insulin resistance

In an effort to unwind the intertwined cascade of FAK, insulin signalling and insulin resistance, during 2007–2008 we have reported studies implicating FAK in the regulation of insulin resistance *in vitro* (Bisht *et al*. 2007; Bisht & Dey, 2008) and *in vivo* (Bisht *et al*. 2008), establishing the role of FAK in regulating insulin resistance.

In order to understand the molecular regulation of insulin resistance, we have developed insulin-resistant C2C12 skeletal muscle cells in our laboratory (Kumar & Dey, 2003). To understand the role of FAK, we approached the problem in two ways i.e. gain of function by overexpessing FAK and loss of function by silencing FAK. A significant decrease in tyrosine phosphorylation of FAK was observed in insulin-resistant C2C12 cells. Overexpression of FAK in insulin-resistant C2C12 skeletal muscle cells increased insulin sensitivity and glucose uptake (Bisht *et al*. 2007). These effects were reversed by expression of kinase activity mutant FAK or suppression of endogenous FAK by siRNA. FAK was also found to interact downstream of IRS-1, phosphatidylinositol 3-kinase (PI3K) and protein kinase C (PKC), leading to glucose transporter-4 (Glut-4) translocation and in up-regulation of glucose uptake. The study demonstrated for the first time, a direct role of FAK in insulin-resistant skeletal muscle cells. However, the underlying mechanism for FAK-mediated Glut-4 translocation leading to glucose uptake still remained unknown. We observed that overexpression of FAK induces actin remodelling and enhances co-localization of Glut-4 with actin, and thus elicits glucose uptake under insulin-resistant conditions (Bisht & Dey, 2008). FAK silencing by siRNA prevented actin remodelling, negatively affecting Glut-4 translocation and resulting in insulin resistance (Fig. 1). Further we observed that FAK regulates Glut-4 translocation via a PI3K-dependent pathway. Our study provided evidence that strongly supports the idea that modulation of FAK expression regulates insulin sensitivity in skeletal muscle cells in culture.

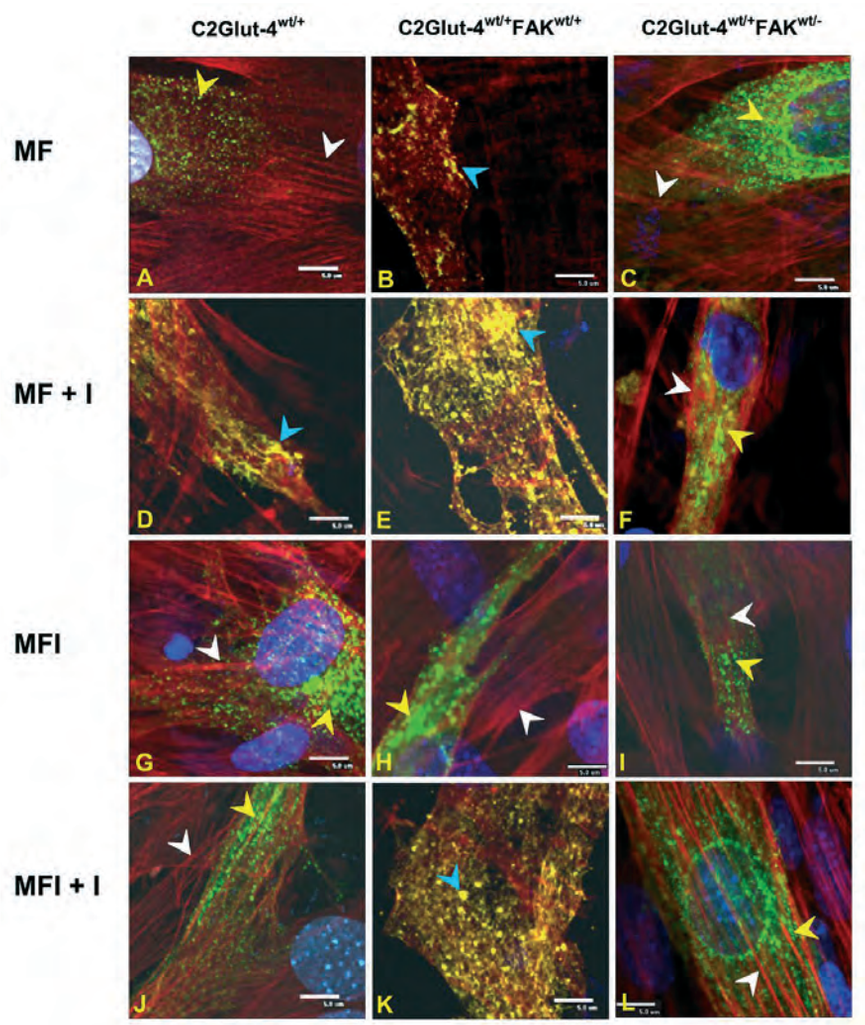

Figure 1. Effect of FAK expression on insulin-mediated actin remodelling and Glut-4 translocation in C2C12 skeletal muscle cells. Glut-4-transfected cells expressing endogenous level of FAK (C2Glut-4$^{wt/+}$), overexpressing FAK (C2Glut-4$^{wt/+}$FAK$^{wt/+}$) and underexpressing (silenced) FAK (C2Glut-4$^{wt/+}$FAK$^{wt/-}$) were differentiated under insulin-sensitive (MF) and insulin-resistant conditions (MFI), serum starved (4 h) and stimulated with and without 100 nM insulin for 30 min at 37°C, followed by fixation and permeabilization. Actin filaments were labelled with Phalloidin Texas Red, nucleus with DAPI. Images were captured from different fields and a representative image of 3 experiments is presented. Bars represent 5 µm. *A*, *B* and *C*: C2Glut-4$^{wt/+}$, C2Glut-4$^{wt/+}$FAK$^{wt/+}$ and C2Glut-4$^{wt/+}$FAK$^{wt/-}$ cells differentiated under insulin-sensitive condition; *D*, *E* and *F*: C2Glut-4$^{wt/+}$, C2Glut-4$^{wt/+}$FAK$^{wt/+}$ and C2Glut-4$^{wt/+}$FAK$^{wt/-}$ cells differentiated under insulin-sensitive conditions, stimulated with insulin; *G*, *H* and *I*: C2Glut-4$^{wt/+}$, C2Glut-4$^{wt/+}$FAK$^{wt/+}$ and C2Glut-4$^{wt/+}$FAK$^{wt/-}$ cells differentiated under insulin-resistant conditions; *J*, *K* and *L*: C2Glut-4$^{wt/+}$, C2Glut-4$^{wt/+}$FAK$^{wt/+}$ and C2Glut-4$^{wt/+}$FAK$^{wt/-}$ cells differentiated under insulin-resistant conditions, stimulated with insulin. White arrowheads represent actin filaments, yellow arrowheads represent Glut-4 molecules and blue arrowheads indicate co-localized actin with Glut-4 (Bisht & Dey, 2008). MF: MCDB201 and Ham's F-12 medium (1 : 1) + 0.5% BSA. MFI: MCDB201 and Ham's F-12 medium (1 : 1) + 0.5% BSA + 100 nM insulin.

To prove conclusively the role of FAK in insulin resistance we down-regulated FAK expression using hydrodynamic tail vein injection of FAK-specific siRNA in mice *in vivo* (Bisht *et al*. 2008). We observed that FAK silencing impaired insulin signalling, altered glucose tolerance associated with weight gain and developed hyperglycaemia and hyperinsulinaemia (Fig. 2). FAK silencing resulted in inhibition of IRS-1 expression which in turn inhibited the downstream pathway leading to impaired insulin signalling. This provided direct and conclusive evidence that FAK is a crucial mediator of insulin resistance *in vivo*.

We believe our findings *in vitro* and *in vivo* will certainly be helpful in understanding the molecular basis

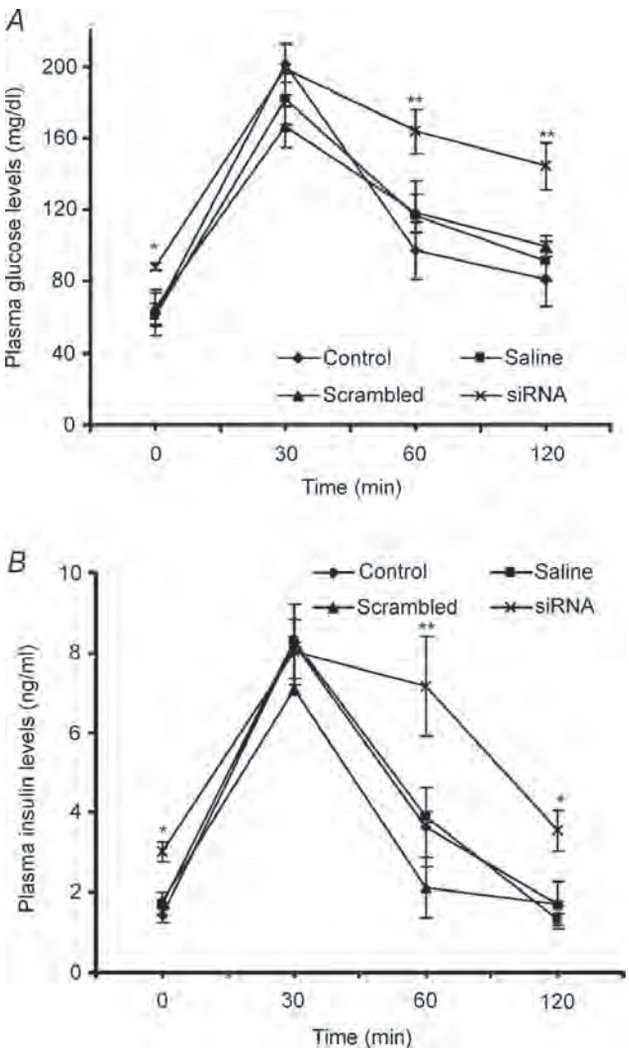

Figure 2. Effect of FAK silencing on glucose tolerance. Male mice (Swiss albino, 10–11 g weight) were injected with 2500 nM of siRNA once weekly for 2 weeks. The glucose tolerance tests (GTT) were performed after 16 h of fasting. *A*, plasma glucose levels after glucose administration at different time intervals. *B*, plasma insulin levels after glucose administration at different time intervals. Data are shown as means ± S.E.M. ($n = 6$). $^{*}P < 0.05$, $^{**}P < 0.01$ (Bisht *et al*. 2008).

of insulin resistance. Considering the lethality of the FAK gene knockout approach, our study will provide a new strategy for *in vivo* inhibition of FAK. Furthermore, the study will certainly motivate chemists to synthesize new chemical entities for FAK activation and promote development of new drugs against insulin resistance.

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Is brain carbohydrate consumption driven by adrenaline?

Many people use exercise to switch the brain off following a stressful day. While low intensity exercise can be performed almost automatically, strenuous exercise requires intense brain activation to keep the muscles working. Brain activation is accompanied by increased carbohydrate uptake and an increase in plasma adrenaline, rather than in noradrenaline, appears to be important for this uptake, suggesting that cerebral glycolysis is driven by a β_2-adrenergic mechanism

Cerebral metabolism at rest

At rest, cerebral energy metabolism is covered almost exclusively by oxidation of glucose since the molar ratio between the brain's oxygen (O_2) uptake to that of glucose is ~6. However, glucose is not the only substrate that supports brain metabolism. Lactate is recognized as an energy substrate for neurons and, therefore, the total amount of carbohydrates taken up by the brain relative to that of O_2 is considered in the O_2–carbohydrate index: OCI [O_2/(glucose + ½ lactate)]. A value of ~5.7 is often reported at rest although OCI may be as low as ~4 (Seifert *et al*. 2009) or above 6.

Cerebral metabolism during exercise

During light exercise OCI is maintained near its resting value, but during intense to maximal exercise, OCI decreases to the lowest reported value of 1.7 during maximal ergometer rowing with an arterial lactate concentration of ~20 mM. The mechanism responsible for the decrease in OCI is not yet established (Dalsgaard, 2003), but OCI decreases independently of O_2 availability. Even though cerebral lactate uptake increases in proportion to the arterial lactate concentration, OCI also decreases in the absense of a significant increase in arterial lactate concentration (<2 mM) during prolonged exercise. Also, the uptake of free fatty acids, glycerol, glutamine, alanine and pyruvate cannot explain the decrease in OCI during cerebral activation. Rather, cerebral glycogen metabolism may explain the decrease in OCI since the glycogen deposit in the brain (~10 μmol g^{-1}) is of the same order of magnitude as the surplus uptake of carbohydrate during intense exercise (Dalsgaard, 2006). During cerebral activation the surplus uptake of carbohydrate could replenish the cerebral glycogen deposit.

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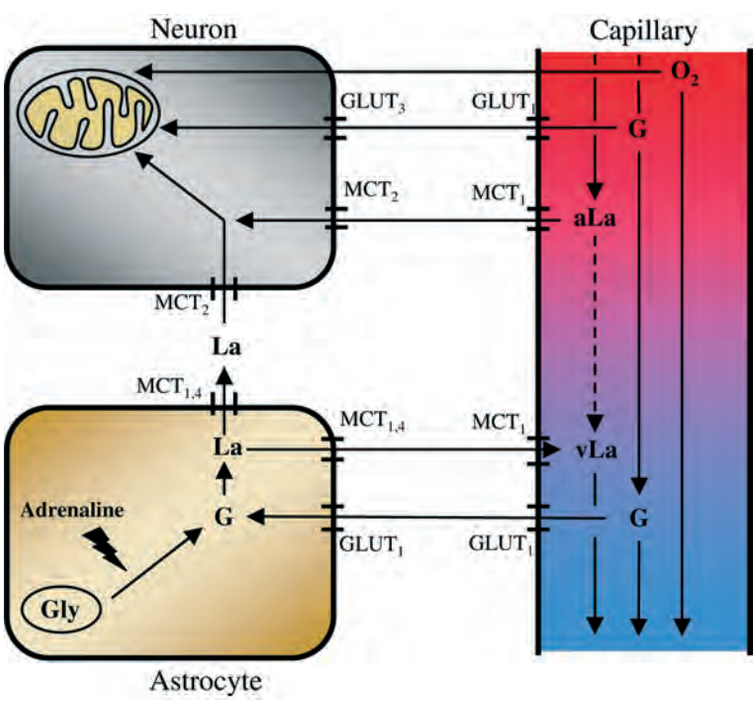

Figure 1. The effect of adrenaline on cerebral carbohydrate metabolism. O_2, glucose (G) and arterial lactate (aLa) are used by the neurons for oxidative energy generation. O_2 diffuses from the capillaries to the neurons, whereas glucose is transported through the vessel membrane and from the interstitium to the neuron via the glucose transporters (GLUT; specific GLUTs indicated). Lactate is transported to the neuron via the monocarboxylate transporters (MCT; specific MCTs indicated) located in the luminal and abluminal membranes of the vessel and in the membrane of the neuron. Glucose is also transported to the astrocyte, where it can be used for glycogen (Gly) synthesis or metabolised to lactate. The intense brain activation required for maximal exercise increases adrenergic glycolysis in astrocytes and glycogen is converted to glucose and lactate. Lactate is either transported to the neurons for oxidation or the circulation eliminates it. At rest there is a net release of lactate, that shifts to an uptake during exercise and, in some situations lactate has a glucose-sparing effect. Intense exercise increases the cerebral metabolic rate of O_2 ~25% related to a Q_{10} effect and the release of lactate from the brain is at least doubled.

In order to accommodate the increased energy demand during cerebral activation, additional glucose and lactate are taken up by the brain to support oxidation in neurons supplemented by glycolysis in astrocytes that provide lactate to neurons for oxidation. Evidence of increased cerebral glycolysis during brain activation is obtained using ^{13}C-labelled lactate to demonstrate a 2-fold increased lactate uptake at an arterial concentration of ~4 mM,

whereas the release is unaffected. However, during exercise with an arterial lactate concentration of ~7 mM, the cerebral lactate uptake increases ~6-fold and the release increases 2-fold (Fig. 1). Since virtually all lactate taken up by the brain is metabolized at rest (~100%) as well as during exercise (~87 %), the increased lactate release from the brain during intense exercise supports the idea that the rate of glycolysis increases with metabolism. Glycolysis may be needed during maximal exercise for which the increase in cerebral O_2 consumption becomes so pronounced that both global and regional cerebral oxygenation decrease to a critical level.

Sympathetic influence on cerebral metabolism ?

The OCI decreases not only during exercise. In a positron emission tomography (PET)-based evaluation of brain metabolism, OCI decreased in the visual cortex from a resting value of 4.1 to 2.8 in response to intense visual stimulation (Fox *et al*. 1988). Similarly, a mental task decreases OCI as determined by arterial and internal jugular venous blood sampling (Madsen *et al*. 1995). Following catheterization, there is some recovery of OCI, e.g. from ~4 to ~5 over an hour (Seifert *et al*. 2009) suggesting that OCI decreases in response to the associated discomfort (Fig. 2). Such a psychological effect could also explain the low baseline OCI of 4.1 in the study by Fox *et al*. (1988), maybe reflecting the anxiety provoked by being placed in a scanner. In support, subjects seem to adapt to participating in an experiment with reduced anxiety, as illustrated by a reduced cerebral carbohydrate uptake and, thus, a higher resting OCI when they visit the laboratory for the follow-up (Fig. 2). At that time, the arterial adrenaline concentration is attenuated.

Together these observations indicate that OCI decreases in response to sympathetic stimulation and OCI decreases in response to infusion of adrenaline at a rate establishing an arterial plasma concentration comparable to that elicited during strenuous exercise (70% of maximal oxygen uptake; VO_2max) during which OCI decreases (Fig. 1; Seifert *et al*. 2009). In contrast, infusion of noradrenaline is without an effect on OCI at an arterial concentration comparable to that established during strenuous exercise. When strenuous exercise is carried out with the β_1/β_2-adrenergic receptor antagonist propranolol, the decrease in OCI is prevented (Larsen *et al*. 2008), whereas the OCI decreases during exercise with the β_1-adrenergic receptor antagonist metoprolol (Dalsgaard, 2006). Thus, circulating adrenaline seems to stimulate cerebral carbohydrate metabolism mediated via a β_2-adrenergic receptor mechanism.

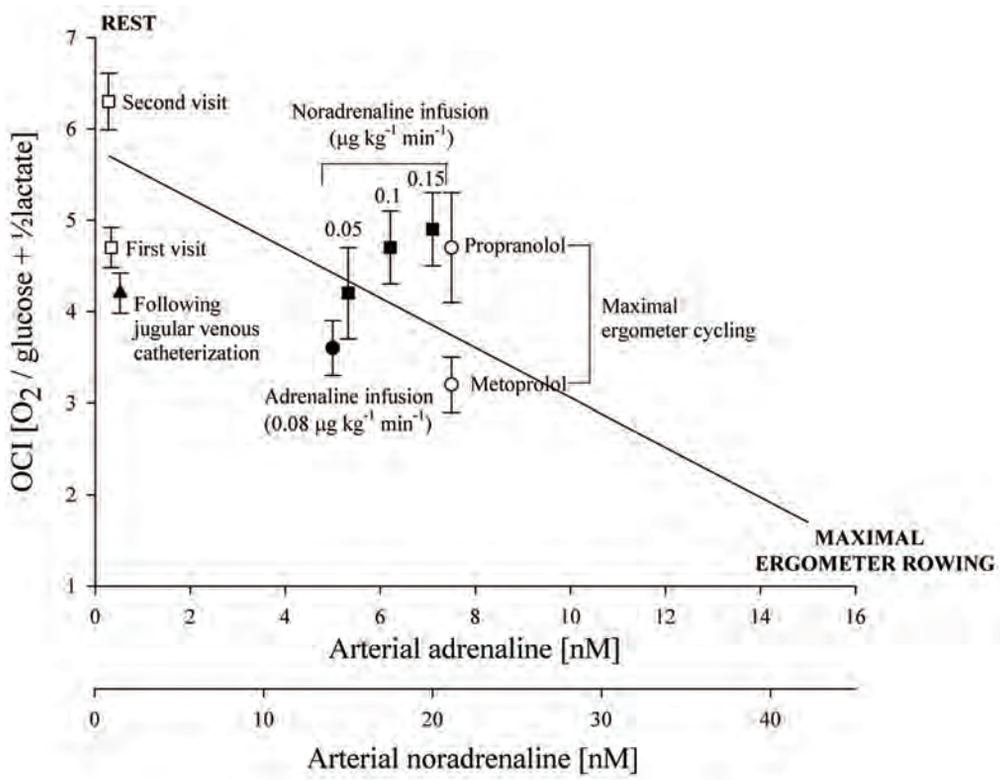

Figure 2. Demonstration of a β_2-adrenergic-dependent decrease in the cerebral oxygen to carbohydrate index (OCI) in response to various levels of sympathetic activity, as indicated by estimates of plasma adrenaline and noradrenaline. The continuous line indicates various exercise-induced decreases in OCI from a resting value of ~5.7 with ergometer rowing representing the extreme low value. Just after catheterization of the internal jugular vein, OCI is ~4 (▲), while for subjects participating in a training study, OCI is higher and the arterial adrenaline concentration lower, when they report to the laboratory for the follow-up (□). Adrenaline (●), but not noradrenaline (■) reduces OCI at rest and to a degree corresponding to the estimated arterial adrenaline concentration during intense exercise. In contrast propranolol, but not metoprolol, prevents the decrease in OCI during maximal ergometer cycling (○).

How does adrenaline affect cerebral carbohydrate metabolism?

How adrenaline exerts its effect on cerebral metabolism remains speculative. A decrease in OCI supports the idea that glycolysis takes place in astrocytes during intense brain activation since the carbohydrate uptake cannot be accounted for by that of O_2 and adrenaline may accelerate cerebral glycogenolysis. The premise for this suggestion is that adrenaline released into the circulation is capable of penetrating the blood–brain barrier. In order to elucidate the role of adrenaline on cerebral carbohydrate uptake, we are awaiting, for example, a tissue culture evaluation of β_2-adrenergic influence on glycogen turnover in astrocytes, thereby revealing whether a decrease in OCI is related to breakdown or replenishment of the cerebral glycogen level.

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Parathyroid hormone-related protein (PTHrP): a modulator of fetal growth and development

The role of PTHrP during embryonic development is slowly being elucidated. Recent data suggest that PTHrP plays a key role in the regulation of placental calcium transport, fetal skeletal development and calcium homeostasis. Our understanding of how PTHrP exerts these effects *in utero* has been improved by studies using genetically modified mice in which fetal expression of PTHrP has been ablated. These investigations have provided insights into the multiple roles of fetal PTHrP in normal embryonic development

In order for a baby to undergo normal development and achieve its growth potential, maintenance of an optimal *in utero* environment is absolutely crucial. Epidemiological evidence has demonstrated that babies of low birth weight, reflecting possible undernourishment during intrauterine life, are at increased risk of various chronic diseases including the development of osteoporosis later in life (Cooper *et al.* 2002). So, is there is a causal relationship between sub-optimal fetal nutrition and aberrant bone development? Observations from animal studies suggest that there is. Maternal protein restriction leads to reduced bone mineral content and bone area in the offspring, with evidence of altered bone morphology and structural strength (Lanham *et al.* 2008). Thus, osteoporosis could be partly programmed *in utero*. To gain a better understanding of the biological mechanisms that link an altered fetal nutrient provision to compromised bone development *in utero,* we first need to elucidate how fetal skeletal development is regulated, particularly as the placenta must 'adapt' its transport function in order to meet the dynamic fetal demand for calcium and mineral provision during skeletogenesis. This demand is most acute over the last third of pregnancy when fetal deposition of calcium rises exponentially. Such an increase in fetal calcium accretion must reflect an increased net calcium flux to the fetus, represented as the difference between the unidirectional maternofetal and fetomaternal fluxes.

Jocelyn Glazier and Mark Dilworth.

Movement of calcium across the placenta is an asymmetric process, with the maternofetal calcium flux predominant, driven by active, transporter-mediated transfer of calcium. The mechanisms involved in maternofetal calcium flux across the epithelium of human placenta, the syncytiotrophoblast, have been modelled as a three-stage process (Fig. 1): calcium entry, cytosolic translocation and exit, in common with the transcellular movement of calcium across other epithelia such as the intestine and kidney. Ca^{2+} in maternal plasma is transported across the maternal-facing microvillous plasma membrane of the syncytiotrophoblast down the favourable electrochemical gradient through epithelial calcium channels of the transient receptor potential vanilloid (TRPV) subfamily, with involvement of TRPV6 implicated. Ca^{2+} is then translocated across the cytosol following binding to

calcium binding proteins which help to buffer intracellular Ca^{2+} whilst facilitating transcellular calcium movement. The molecular identities of the calcium binding proteins involved in this process in human placenta are not well defined, as several calcium binding proteins are expressed. However, in rat placenta and mouse placenta, calbindin-D_{9K} is particularly important as shown by the marked increase in placental expression of calbindin-D_{9K} over the last third of pregnancy and its stoichiometric relationship with the rise in maternofetal calcium flux (Glazier *et al.* 1992; Bond *et al.* 2008). In these species, at least, placental calbindin-D_{9K} expression may be rate-limiting to placental calcium transport. Ca^{2+} is then transported across the fetal-facing basal plasma membrane (BM) of the syncytiotrophoblast against the electrochemical gradient to the fetus. This occurs through the actions of the plasma membrane Ca^{2+}-ATPases (PMCAs) localised to the BM. PMCA1 and PMCA4 isoforms have been demonstrated in placenta (Strid & Powell, 2000; Bond *et al.* 2008). The upregulation of PMCA activity in BM over the last trimester of human pregnancy (Strid & Powell, 2000) would serve to promote fetal provision of calcium at a time of great fetal demand.

PMCA activity in BM can be stimulated by physiological concentrations of PTHrP (38–94 amide), but not by PTHrP (1–34), PTHrP (67–86) or PTH at comparable concentrations (Strid *et al.* 2002). Calcium transfer into the fetal circulation of the *in situ* perfused placenta of parathyroidectomised or thyroparathyroidectomised fetal lambs was also stimulated by the addition of partially purified hPTHrP or recombinant PTHrP(1–84), PTHrP(1–108), PTHrP(1–141), hPTHrP (75–84), hPTHrP(67–86 amide) and hPTHrP(75–86 amide) but not by synthetic PTHrP(1–34) (Abbas *et al.* 1989; Care *et al.* 1990). By contrast, infusion of hPTHrP(1–34) or hPTHrP(75–86)amide into the fetoplacental circulation of intact rat fetuses had no effect on placental calcium transport (Shaw *et al.*1991). These observations, although not consistent between studies, do raise the possibility that PTHrP can act to modulate placental calcium transport and highlight that these effects are PTHrP fragment specific. As PTHrP has the ability to act in an endocrine, paracrine, autocrine as well as intracrine manner, the question arises whether PTHrP produced by the maternal (uterine) and/or fetal (from placenta and fetal tissues) compartments of the uteroplacental unit are involved in such regulation?

We (Bond *et al.* 2008), and others (Kovacs *et al.* 1996; Tucci *et al.* 1996), have explored this issue further by examining fetal calcium homeostasis and placental calcium transport in mice with deletion of the PTHrP gene ($PTHrP^{-/-}$), whereby the fetal source of PTHrP is eliminated. $PTHrP^{-/-}$ fetuses exhibit chondrodysplasia characterised by the premature and inappropriate ossification of the developing skeleton with skeletal abnormalities apparent, such as a domed skull, short snout and mandible, and shortened upper and lower limbs. One intriguing feature of these animals is that despite the broad tissue distribution of PTHrP, skeletal morphogenesis is most notably affected whilst other tissues show no gross morphological abnormalities (Karaplis *et al.* 1994). $PTHrP^{-/-}$ fetuses are modestly growth-restricted with an ~6% reduction in fetal weight compared to their wild-type littermates (Kovacs *et al.* 2001; Bond *et al.* 2008) and have a significantly reduced blood ionised $[Ca^{2+}]$ resulting in the abolition of the fetomaternal calcium gradient (Kovacs *et al.* 1996; Tucci *et al.* 1996; Bond *et al.* 2008). Near term, they have a significantly higher calcium content than wild-type littermates (Tucci *et al.* 1996; Bond *et al.* 2008), implying that the net flux of calcium across the placenta to the fetus has been increased.

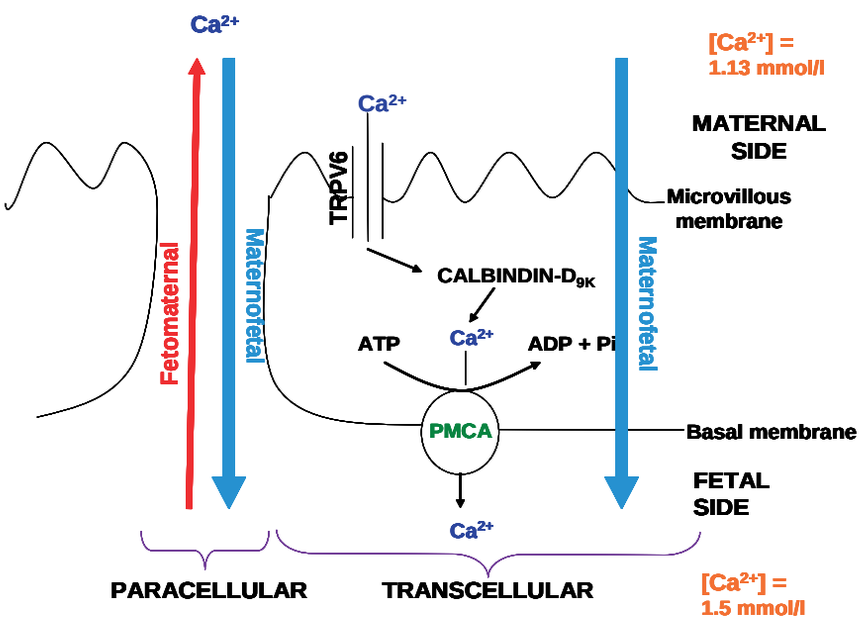

Figure 1. Schematic showing mechanisms of Ca^{2+} transport across the human placenta (which could be applied generically to other species). Calcium enters the syncytiotrophoblast across the maternal-facing microvillous plasma membrane down a favourable electrochemical gradient via the calcium channel TRPV6. Calcium binds to the calcium binding protein (most probably calbindin-D_{9K}) which mediates the transcytosolic movement of calcium. Calcium is extruded across the fetal-facing basal plasma membrane by the action of PMCA. This active transport of calcium results in a fetal ionised calcium concentration significantly higher than maternal. Calcium flux is highly asymmetric with the maternofetal calcium flux prevailing (bigger arrow) whilst the fetomaternal flux of calcium is comparatively small (smaller arrow). TRPV6, transient receptor potential vanilloid type 6 channel; PMCA, plasma membrane calcium ATPase.

To elucidate this further, we measured the unidirectional maternofetal clearance of calcium ($^{Ca}K_{mf}$) across the perfused and intact placenta of PTHrP$^{-/-}$ fetuses compared to wild-type at embryonic day 18 (Bond *et al.* 2008). These studies demonstrated that $^{Ca}K_{mf}$ was significantly raised in PTHrP$^{-/-}$ fetuses whilst calcium flux in the reverse direction, measured as unidirectional fetoplacental clearance of calcium, was unaffected. This stimulation of placental calcium transport appears to be underscored by an upregulated placental expression of calbindin-D_{9K} (Bond *et al.* 2008). Our data differ from the earlier work of others who showed that, when compared to a marker of diffusion (^{51}Cr-EDTA), $^{Ca}K_{mf}$ was reduced in PTHrP$^{-/-}$ fetuses, accompanied by a decrease in placental calbindin-D_{9K} expression and unaltered fetal calcium content (Kovacs *et al.* 1996). The possible reasons for this have been fully debated previously (Bond *et al.* 2008).

These studies have clearly demonstrated that fetal PTHrP plays a pivotal role in maintaining the hypercalcaemic status of the fetus relative to the mother. The excessive skeletal mineralization and premature calcification/ossification found in PTHrP$^{-/-}$ fetuses raises the possibility of an elevated fetal calcium demand. This appears to stimulate maternofetal calcium transport by the induction of placental calbindin-D_{9K} expression. The stimuli that drive this response are unknown, but may be multifactorial (Bond *et al.* 2008).

The widespread tissue expression of PTHrP during fetal life strongly implicates PTHrP as a key regulator of developmental processes that influence fetal growth. In the light of the observations described here, the notion that PTHrP serves as a linchpin in the programming of bone development by *in utero* environment is certainly worthy of further investigation.

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Many scientists take a career break, for example for family reasons. Returning to the lab after a few years absence can be a daunting prospect, given the speed with which science and technologies progress. Daphne Jackson was Britain's first female professor of physics and a lifelong campaigner, encouraging women into engineering and science. In 1985 she began a pilot scheme to return women to science engineering and technology (SET) careers. The Daphne Jackson Trust (www.daphnejackson.org) was set up after her death to continue her work.

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Calcium: it's not just for bones!

Calcium ions in the human body have diverse physiological functions. Recently, extracellular calcium ions and a G protein-coupled, calcium-sensing receptor have been shown to play a role in developmental lung physiology. By increasing our knowledge of the lung development process, we may be able to pursue novel treatments that could improve outcomes for infants born prematurely or born with developmental lung disorders

Calcium is an ion with diverse roles

When talking with friends and family, if you say that you work with calcium ions, most automatically assume that you also work with bones. Correct this assumption to tell them that you are looking at the effects of Ca^{2+} on lung development and their next question becomes, 'There is calcium in the lungs?' The answer to this question is, of course, 'There is calcium throughout the body'. There are many processes, from the formation of bones to the contraction of muscles and beyond, that are dependent upon Ca^{2+}.

Aside from its direct actions, Ca^{2+} can act as a signalling molecule through a G protein-coupled receptor called the calcium-sensing receptor (CaR). Indeed, our bodies maintain a constant systemic free-ionised extracellular Ca^{2+} concentration ($[Ca^{2+}]_o$) by integrating the actions of several tissues including the parathyroid gland, intestine, kidney and bone. In the adult, parathyroid CaR keeps systemic $[Ca^{2+}]_o$ at approximately 1.2 mM. In the fetus, $[Ca^{2+}]_o$ is higher than in the mother, as reported in mice, sheep and humans. The fetal CaR is involved in the maintenance of this relative hypercalcaemia, which lasts throughout gestation, and is resolved to normocalcaemia within 24 hours after birth (Kovacs *et al.* 1998). While late in gestation the majority of Ca^{2+} obtained by the fetus is deposited in the developing skeleton, other physiological effects of this relative hypercalcaemia during development, are only recently emerging. In our study (Finney *et al*. 2008), we have shown that Ca^{2+}_o is an important, extrinsic factor which regulates several aspects of the intrinsic developmental programme of the lung.

Calcium and lung development

In order to meet its primary function after birth – gas exchange – the developing lung must undergo a process of branching, growth and differentiation. These processes are accompanied by airway peristalsis, stereotypic branching morphogenesis and chloride secretion into a fluid-filled lumen (Fig. 1*A*). Together, these events ensure that there is a correct number of optimally distended terminal airway buds which contain the requisite cellular components so that the emerging fetus can efficiently take its first breath.

From left to right: Daniela Riccardi, Brenda Finney, Paul Kemp and William Wilkinson.

In embryonic rat lungs, the airway smooth muscle (ASM) lining the basal side of the developing airway epithelium, exhibits spontaneous peristaltic movements which are dependent on an intracellular Ca^{2+} (Ca^{2+}_i) wave originating from a pacemaker region in the right proximal lung. This phenomenon, which is dependent upon Ca^{2+}_o influx, can be correlated with fetal lung growth, that is, an increase in lung growth causes an increase in peristalsis, and a decrease in peristalsis decreases lung growth (Jesudason *et al.* 2005). Ca^{2+}_i imaging

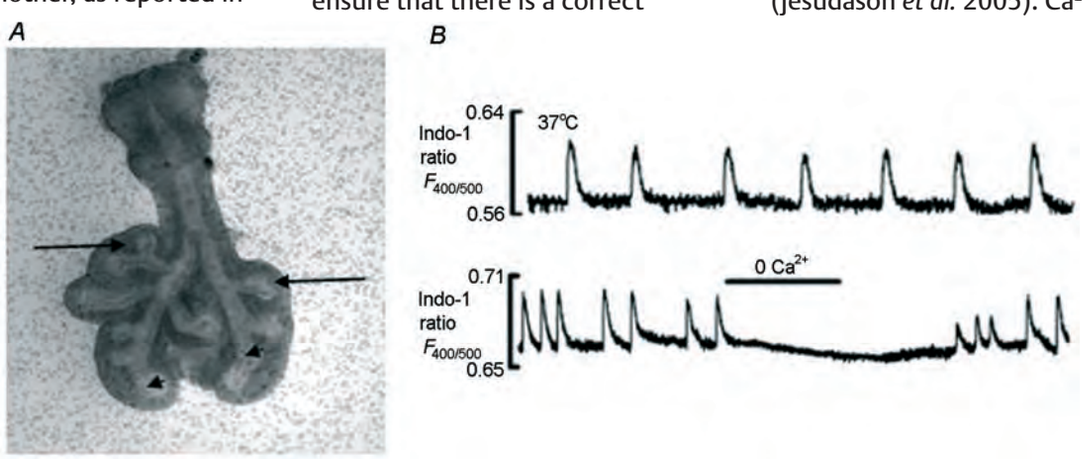

Figure 1. *A*, exemplar E12.5 mouse lung at time of placement into culture. Arrows indicate branching points of terminal buds, arrowheads indicate fluid-filled lumena. *B*, intracellular Ca^{2+} waves in airway smooth muscle of the developing lung are regular (top trace) and are initiated from a pacemaker region in the right proximal lung. These waves can be abolished when Ca^{2+}_o is removed from the bath solution, but restart when Ca^{2+}_o is re-introduced (bottom trace). Panel *B* reproduced with permission from Featherstone *et al.* 2005.

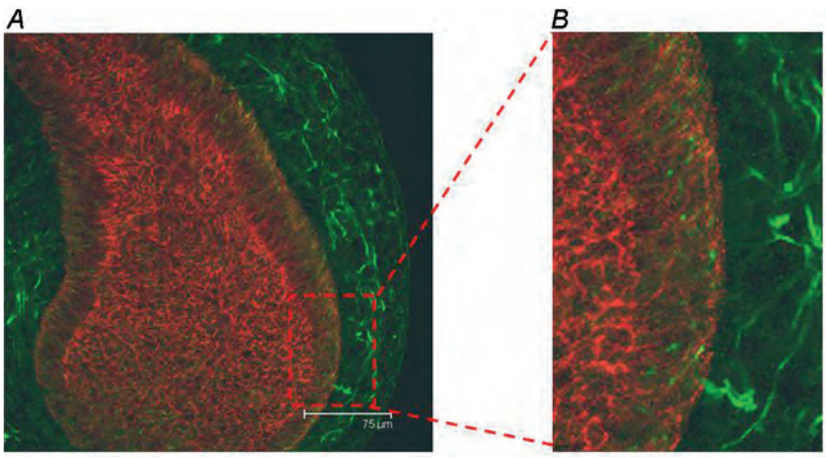

Figure 2. *A*, CaR is detected in the E11.5 mouse lung by immunofluorescence. CaR expression (green fluorescence) is detected in both the epithelium (co-localised in cells which express the epithelial marker, E-Cadherin – red fluorescence) and the mesenchyme. Scale bar, 75 µm. *B*, higher magnification of red boxed area to show detail of CaR expression in both the epithelium and the mesenchyme.

has revealed that regenerative, spontaneous waves (Fig. 1*B*, top trace) travel via gap junctions through the ASM. Nominally Ca^{2+}_o-free solution applied to cultured lung explants causes both the Ca^{2+}_i signalling and peristalsis to cease completely (Fig. 1*B*, bottom trace), but these processes restart when Ca^{2+}_o is reapplied (Featherstone *et al.* 2005). Therefore, both Ca^{2+}_o and Ca^{2+}_i signalling are vital components of ASM peristalsis and the growth of the developing lung. While these studies show that both the presence of Ca^{2+}_o and Ca^{2+}_i signalling are necessary, there is no information regarding how the chronically elevated $[Ca^{2+}]_o$ of the fetus may effect lung growth and development.

Recently, we have found that the CaR is expressed and active during mouse lung development (see Finney *et al.* 2008 and Figs 2 and 3). This receptor exhibits a developmentally regulated pattern of expression which peaks at the time corresponding to lung branching morphogenesis. Using serum-free, chemically defined medium containing 1.7 mM Ca^{2+}_o (corresponding to $[Ca^{2+}]_o$ in late gestation, fetal plasma), embryonic day 12.5 mouse lungs cultured for 48 hours undergo significantly less branching morphogenesis than that achieved by explants grown in the presence of adult $[Ca^{2+}]_o$ (1.05–1.2 mM, Fig. 3*A* and *B*). Activation of the CaR with a specific positive allosteric modulator of the receptor, R-568, mimics the effects of the higher $[Ca^{2+}]_o$ in that it too restricts the rate of branching morphogenesis. This CaR-dependent control of branching occurs through phospholipase C and phosphotidylinositol 3-kinase signalling pathways. Additionally, secretion of chloride into the lung lumen, a vital part of forming the liquid template around which the lung branches grow, is also affected by Ca^{2+}_o and CaR activation. Thus, chloride secretion, measured as transepithelial potential difference,

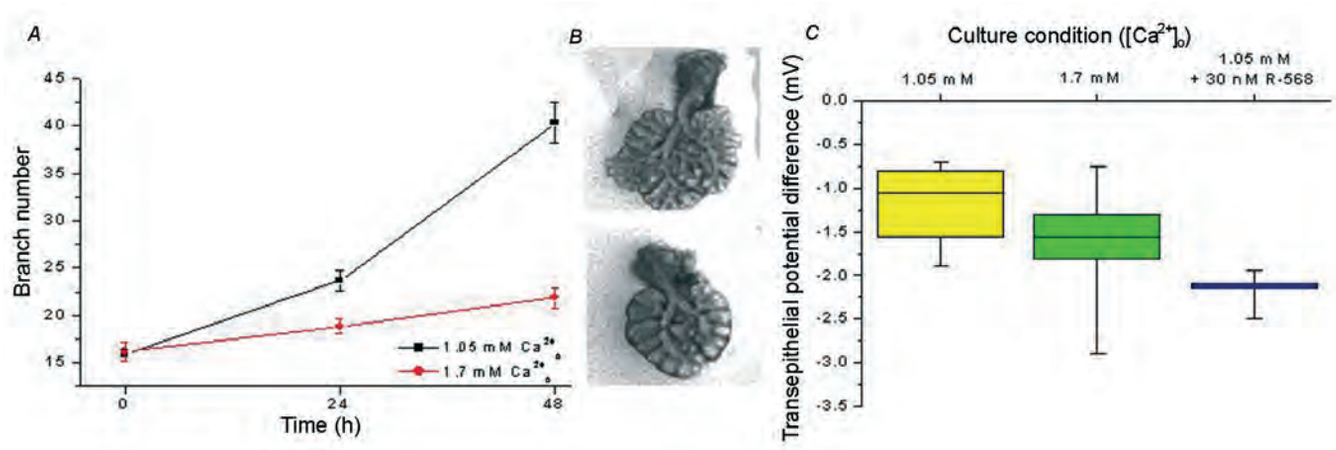

Figure 3. *A*, lung branching morphogenesis is sensitive to $[Ca^{2+}]_o$. In the presence of low $[Ca^{2+}]_o$ (i.e. 1.05 mM, black squares) in a greater number of terminal branches, after both 24 and 48 h in culture, are seen than in the presence of the higher $[Ca^{2+}]_o$ (i.e. 1.7 mM, red circles). *B*, exemplar lungs from each of the culture conditions. Top panel, an E12.5 mouse lung grown in the presence of 1.05 mM Ca^{2+}_o for 48 h. Bottom panel, an E12.5 mouse lung grown in the presence of 1.7 mM Ca^{2+}_o for 48 h. *C*, transepithelial potential difference is used to assay epithelial Cl^- secretion into the developing lung lumen. When lungs are cultured in the presence of either 1.7 mM Ca^{2+}_o (green bar) or 1.05 mM Ca^{2+}_o + 30 nM R-568 (blue bar, positive allosteric modulator of CaR) for 48 h, the transepithelial potential difference is more negative than when lungs are cultured in the presence of 1.05 mM Ca^{2+}_o (yellow bar) for 48 h.

is higher in the presence of 1.7 mM Ca^{2+}_o than it is in 1.05 mM Ca^{2+}_o, and it is increased even further upon specific activation of the CaR by R-568. (Fig. 3*C*).

These data are the first demonstration that Ca^{2+}_o, acting through the CaR, have long-term effects on lung development. These data imply that $[Ca^{2+}]_o$ and CaR-dependent signalling are involved in the formation and expansion of peripheral airways. Our initial interpretation of these data is that CaR activation at fetal $[Ca^{2+}]_o$ (approximately 1.7 mM) acts as a physiological brake on branching morphogenesis while enhancing chloride secretion. The physiological significance of these opposing effects may be to ensure matching of airway branching with expansion to optimise the gas transfer interface.

The importance of getting lung development right

Perturbations of the developmental programme which impinge upon this important developmental balance can result in decreased functionality of the postnatal lung. Disruption of lung development can be caused by malformations of the chest cavity, exposure to toxins, inappropriate gene expression, fetal growth restrictions or premature birth. Premature birth is a significant problem which inherently carries with it the risks of inadequate lung development. The inadequacies of the premature lung are exacerbated by instances of respiratory disease such as respiratory distress syndrome (RDS) or bronchopulmonary dysplasia (BPD; Warburton & Bellusci, 2004).

Indeed, RDS is a major cause of morbidity and mortality in premature infants. In the UK for the year 2001, 58% of newborn deaths occurring before the infant had reached 28 days old were due to RDS or an extremely low weight at birth (National Office of Statistics, http://www.statistics.gov.uk/pdfdir/chi0303.pdf). There is also evidence to suggest that children who are born prematurely and suffer RDS or BPD have a higher incidence of respiratory illness, as well as decreased respiratory flow and diffusion capacity later in life (Moss, 2006).

Along with the physical symptoms detailed above, there are significant socio-economic impacts of prematurity which can last for the lifetime of the affected individuals. In order to reduce the number of deaths and improve the outcomes for these individuals, we must first understand normal developmental lung physiology. By incorporating our new data regarding Ca^{2+} and CaR signalling into the established paradigms of developmental lung physiology, we may be one step closer to ameliorating the suffering of many infants and adults by the development of interventions that could promote the formation of healthy lungs.

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

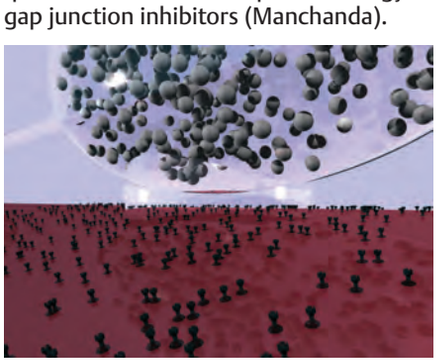
Tuesday 1–Friday 4 September 2009, Sydney, Australia

Chairpersons:
Keith Brain & James Brock

Invited Speakers:
James Galligan
William Dunn
Rohit Manchanda

Burnstock, Holman, Bennett, MacLachlan and Brock are some of the names one might associate with both autonomic junctional transmission and Australia. It is therefore fitting that ISAN2009 in Sydney should include a symposium exploring the regulation of sympathetic transmission.

The symposium will explore recent and emerging issues in junctional transmission, including presentations on a comparison of transmission in arteries and veins in DOCA–salt hypertension (Galligan), a focus on sympathetic junctional transmission in pressurised vessels (Dunn), and some important questions related to the pharmacology of gap junction inhibitors (Manchanda).



So, for those of you with an interest in autonomic junctions, or sandy beaches, perhaps we will meet in sunny Sydney sympathetically to explore transmission.

The generous support of The Physiological Society in supporting this symposium is gratefully acknowledged.

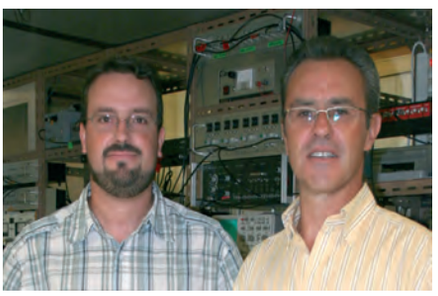
The conference web site is:
www.iceaustralia.com/isan2009/

K Brain

Where do we look while sleeping?

The question of whether rapid eye movements during sleep are similar to those during alertness has been controversial. Recently, a precise description of eye movements and the behaviour of extraocular motoneurons during the wake–sleep cycle has shown that the oculomotor system is controlled by tonic and phasic signals that fully explain eye movements during sleep. Tonic inhibition and a complex pattern of bilateral activation–inhibition of extraocular motoneurons are responsible for the exclusive characteristics of rapid eye movements during sleep

More than 50 years ago, Aserinsky & Kleitman (1953) reported for the first time the existence of periods with fast and jerky eye movements during sleep, thereby defining a new state that has been named active, paradoxical, or – most generally – rapid eye movement (REM) sleep. The same laboratory observed that REM sleep coincided with periods of dreams with high visual content, and in some studies the researchers found a relationship between the direction of eye movements and the subjects' reports about what they were seeing during dreaming (Dement & Kleitman, 1957). Thus, eye movements during REM sleep were considered to be related to the exploration of visual scenes during dreaming.



Javier Márquez-Ruiz (left) and Miguel Escudero (right).

However, the recording of new variables during REM sleep revealed the existence of other phasic phenomena such as high-amplitude spiky potentials – ponto-geniculo-occipital (PGO) waves, recorded mainly at the pons, the lateral geniculate nucleus and the occipital cortex (Jeannerod *et al*. 1965) – and sporadic muscular twitches (Chase & Morales, 1983), both occurring in coincidence with bursts of rapid eye movements. These observations, together with the regularity in frequency, amplitude and velocity of rapid eye movements recorded in different species, pointed to the possibility that rapid eye movements could result from automatic activations not merely related with visual scanning during dreaming.

To resolve between these two possibilities, it is necessary to know the precise characteristics of eye movements and the mechanisms

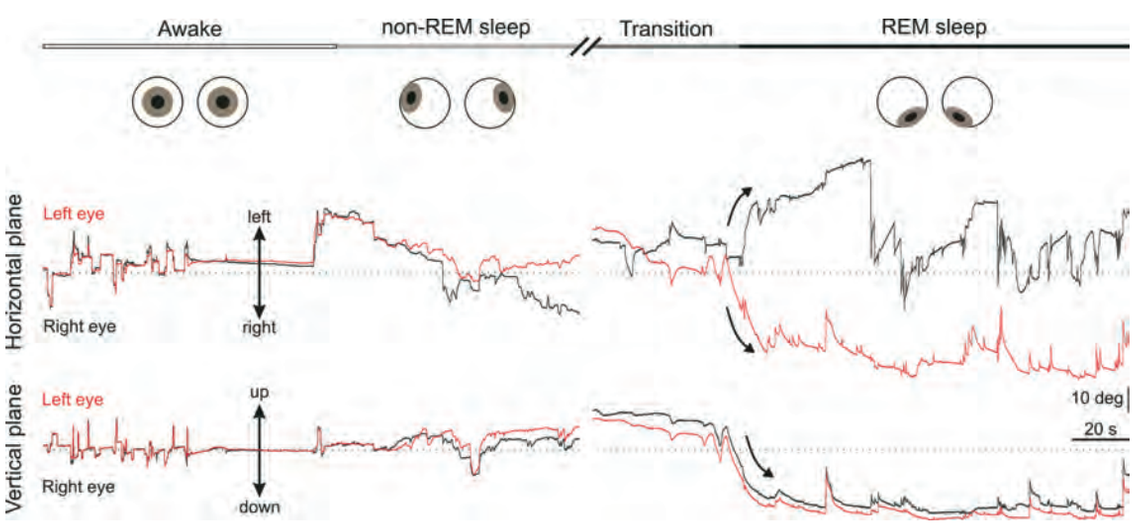


Figure 1. Eye movements during the sleep–wake cycle in cats. Representative recording of left and right (in red and black, respectively) eye movements in the horizontal and vertical plane along the sleep–wake cycle. Polysomnographic recordings enabled the distinguishing of four different periods in the sleep–wake cycle (horizontal bar at the top): awake, non-REM sleep, period of transition to REM sleep, and REM sleep. A schematic representation of binocular position is presented beneath to facilitate comparison between different oculomotor behaviour during each period. During alertness, eye movements were conjugated and were characterised by fixations interrupted by saccades that moved the eye from one visual target to another. During non-REM sleep, eye movements were of low velocity and non-conjugated, leading the eyes to a mean divergent and upward position. During REM sleep, the eyes performed bursts of movements of high amplitude and velocity that were greater in the horizontal plane. During REM sleep, the right eye deviated to the left and the left eye to the right (curved arrows in horizontal eye-position traces), generating a tonic convergence. In the vertical plane, the two eyes rotated strongly downward (curved arrow in vertical eye-position traces), and all rapid eye movements in this plane were directed upward. Dotted lines in eye-position traces indicate the centre of the orbit.

by which rapid eye movements are generated during sleep compared to alertness. Until now, with very few exceptions, the most popular technique used to record eye movements has been electrooculography, a technique that although easy to implement during sleep, has a very low spatial resolution and does not yield information about eye position in the orbit or the dynamics of the small eye movements. This, besides an almost complete absence of recordings of neuronal activity in the oculomotor system during sleep, has resulted in a continuing confusion about the nature of eye movements during sleep.

It is paradoxical that the key phenomenon that denominates one of the phases of sleep is the least known of all the classical signs of REM sleep, and even more so when the oculomotor system is probably the most-studied and best-known motor system. In 1963, Robinson introduced the scleral search-coil technique into oculomotor research. This technique determines the exact position of the eye in the orbit even when the eyelids are closed, and is an excellent tool for investigating the physiology of the oculomotor system.

Regarding the motor output of the oculomotor system, the movement of each eye is controlled by the action of six extraocular muscles. Lateral and medial recti control eye movements exclusively in the horizontal plane, while superior and inferior recti and superior and inferior oblique muscles are involved in the control of vertical and torsional movements. Abducting and adducting movements are controlled by abducens (ABD) and oculomotor nucleus, respectively. Internuclear interneurons in the ABD nucleus project to the contralateral oculomotor nucleus, allowing conjugated eye movements in the horizontal plane.

Two recent papers from our laboratory published in *The Journal of Physiology* provide important detail about the nature of eye movements during the sleep–wake cycle, as well as their relationship with the rest of tonic and phase phenomena. In these studies, we recorded binocular eye movements by the scleral search-coil technique (Márquez-Ruiz & Escudero, 2008) and the activity of identified motoneurons of the ABD nucleus (Escudero & Márquez-Ruiz, 2008) in adult cats.

Eye movements during alertness consisted of conjugated saccades and eye fixations (Fig. 1, awake). During non-REM sleep, the two eyes slowly rotated upwards and in the abducting direction, producing a tonic divergence and elevation of the visual axis (Fig. 1, non-REM sleep). During the transition period between non-REM and REM sleep, rapid, low-amplitude monocular eye movements in the abducting direction occurred in coincidence with PGO waves (Fig.1, transition). In REM sleep, the eyes tended to maintain a tonic convergence and depression, broken by high-frequency bursts

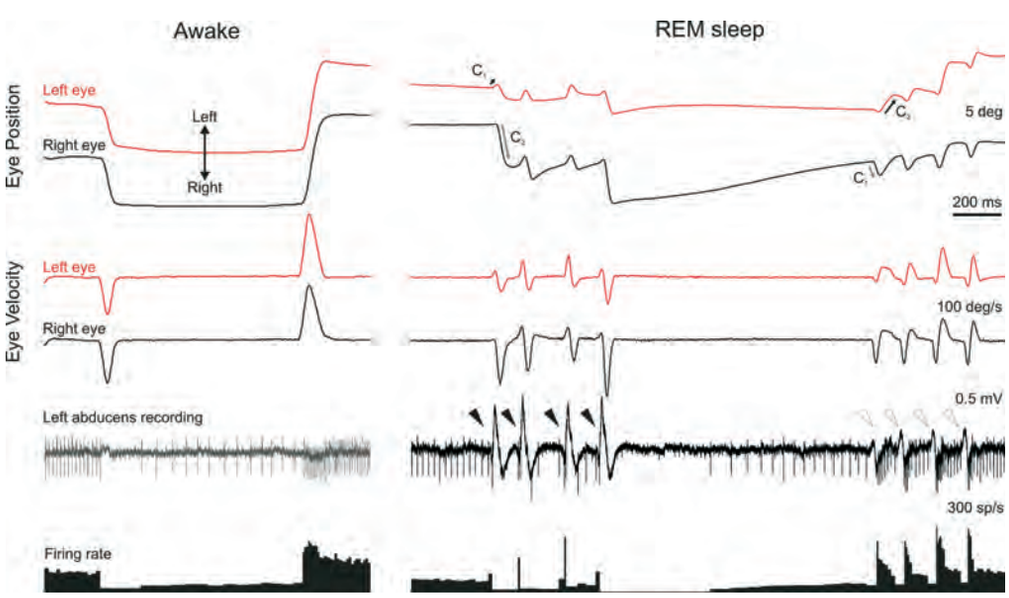


Figure 2. Activity of abducens motoneurons during wakefulness and rapid eye movement (REM) sleep. During wakefulness (left), abducens motoneurons showed a burst, and a tonic firing rate that was proportional to the velocity and position of the ipsilateral eye during movements in the abducting direction. During REM sleep (right), the abducens motoneuron activities were dependent on the occurrence of ponto-geniculo-occipital (PGO) waves. During triphasic PGO waves recorded at the abducens nucleus (filled arrowheads), motoneurons produced a very short burst followed by a pause in their discharge. This short burst produced a short ipsilateral movement of high velocity in the ipsilateral eye (C1). During biphasic PGO waves (open arrowheads), motoneurons paused in their firing discharge, followed by a burst and tonic discharge. This activity induced an ipsilateral movement of the ipsilateral eye (C2) which tended to maintain the position reached. By contrast, the contralateral eye tended to drift to the position it had initially before the rapid eye movement.

of complex rapid eye movements (Fig. 1, REM sleep). In the horizontal plane, each eye movement in the burst comprised two consecutive movements in opposite directions (Fig. 2, see C_1 and C_2 at right), which were more evident in the eye that performed the abducting movements. In the vertical plane, rapid eye movements were always upward.

The activity of ABD motoneurons during REM sleep was characterised by a tonic decrease of their mean firing rate throughout this period, and short bursts and pauses coinciding with the occurrence of PGO waves (Fig. 2, at bottom). We demonstrate that the decrease in the mean firing discharge was due to an active inhibition of ABD motoneurons, and that the occurrence of primary and secondary PGO waves induced a pattern of simultaneous but opposed phasic activation and inhibition in each ABD nucleus. With regard to eye movements, during REM sleep, ABD motoneurons failed to codify eye position as during alertness, but continued to codify eye velocity.

Comparisons of the characteristics of eye movements during the sleep–wake cycle reveal the uniqueness of eye movements during sleep, and the noteworthy existence of tonic and phasic phenomena in the oculomotor system, not observed until now. The pattern of tonic inhibition and the phasic activations and inhibitions shown by ABD motoneurons coincide with those reported in other non-oculomotor motoneurons (Chase & Morales, 1983), indicating that the oculomotor system – contrary to what has hitherto been accepted – is not different from other motor systems during REM sleep, indicating that all motor systems are receiving similar command signals during this period, and therefore that bursts of rapid eye movement during REM sleep are not directly related to the scanning of images while dreaming. On the other hand, the oculomotor system has been found to be an excellent model for the study of motor control during sleep, enabling accurate recording of the motor output (by the search-coil technique) and the motor and premotor neuronal activity inside the brainstem in a well-characterised system. This new model could throw new light on some human pathologies, such as the risk of myocardial ischaemia or arrhythmia or narcolepsy, in which the phasic and tonic activities during REM sleep are relevant.

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No peace for monkey mothers

Every parent is familiar with the feelings experienced when a child throws a public tantrum, and all too often the presence of scowling, disapproving strangers leads them to give in to the outburst. A new study of rhesus monkeys provides the first evidence that a similar effect is seen among our primate cousins (Semple *et al*. 2009). Bystanders affect the outcome of mother–infant interations in rhesus macaques. *Proc Biol Soc* **276**, 2257–2262).

Rhesus mothers are much more likely to give in to their offspring's tantrums when there are potentially aggressive animals nearby. Indeed, it appears that it is the threat of violence from these nearby animals that tips the balance in favour of the screaming infants, and forces mothers to acquiesce to their demands.

Stuart Semple of Roehampton University and his colleagues made these new discoveries while studying a population of rhesus monkeys living on Cayo Santiago, an island off the coast of Puerto Rico. The crying of rhesus monkey infants – just like that of human babies – is high pitched, grating and unrelenting.

While these cries are directed at mothers, nearby animals share the pain, and these onlookers often resort to violence to bring the earache to an end. Semple and his team found that both mothers and infants were over 30 times more likely to receive aggression during crying bouts than when infants were silent. Perhaps as a result of this threat, mothers are more than twice as likely to give in to their bawling babies when there were animals nearby that could turn nasty.

The study also found that mothers are prone to losing their cool when faced with screaming infants on one side and irritated onlookers on the other: mothers are over 400 times more likely to be aggressive to their infants when they are crying than when they are quiet.

The peri-conceptional origins of the life-long physiological consequences of being a twin

Studies in twins, both human and ovine, suggest that the fetal developmental trajectory in twins is different from that of singletons and may be reflected by altered physiology in post-natal life. The early pregnancy environment may be critical in determining both pregnancy outcome and the risk for adverse long-term health outcomes

Frank Bloomfield.

Pregnancy outcome in twins

The incidence of twin (and higher order multifetal) pregnancies is increasing worldwide, largely due to increased use of assisted reproductive techniques and advancing maternal age. Twins are born both earlier and smaller than singletons with a mean gestation length of 37 weeks compared with 40 weeks in singletons. The reduced size at birth in twins is not only due to their shorter gestational length; rather, twins have a different birth-size distribution (affecting weight, length and head circumference) from singletons and this persists into childhood.

In essence, therefore, twins could be considered to have constrained fetal growth in that they fail to grow to their genetic potential. This is also the definition of intrauterine growth restriction (IUGR). Do a mean gestational length decrement of 3 weeks, and a shift to the left in distribution of birth size in twins matter?

The consequences of being a twin for short- and long-term health outcomes

Newborn twins have a higher incidence of most common neonatal problems, with mortality and disability rates increased 5- to 10-fold compared with those of singletons. Much of the increased risk can be attributed to preterm birth or IUGR, with even late preterm birth (birth at 34–36 weeks gestation) now recognised as carrying significantly increased risks for a variety of adverse outcomes, including not only physiological parameters such as blood pressure and glucose tolerance, but also developmental progress and school achievement (Morse *et al.* 2009).

The associations between reduced size at birth and a large range of adverse health outcomes in adulthood are now well established in singletons. However, the literature on these associations in twins is much less clear. This may be due in part to classical methodological approaches in twin studies, which entail comparisons of outcomes between monozygotic and dizygotic twins to separate the effects of genes *versus* environment. However, when the effects of the intrauterine environment on outcome are being studied, this separation is

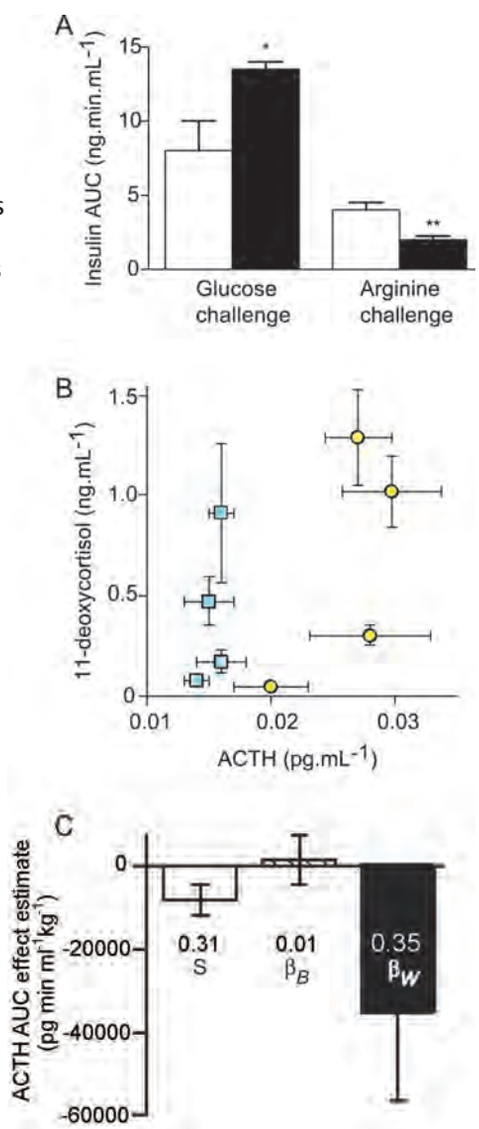

Figure 1. *A*, insulin area under the curve (AUC) in response to a glucose load (left bars) and to arginine stimulation (right bars) in singleton (white bars) and twin (black bars) ovine fetuses in late gestation. $^{*}P < 0.05$, $^{**}P < 0.001$ *vs* singleton fetuses. The increased insulin response to glucose, but decreased response to arginine, is consistent with advanced pancreatic maturation as the beta cells switch from fetal sensitivity to amino acids to mature sensitivity to glucose. *B*, ACTH (*x*-axis) and 11-deoxycortisol (*y*-axis) responses to metyrapone in singleton (blue squares) and twin (yellow circles) ovine fetuses in late gestation. Metyrapone blocks the rate-limiting enzyme for cortisol biosynthesis, resulting in elevation in ACTH and then 11-deoxycortisol (the cortisol precursor) in response to a fall in negative feedback inhibition. Note the increased ACTH concentrations required to achieve a given 11-deoxycortisol concentration in twin fetuses, consistent with adrenal resistance to ACTH ($P < 0.0001$). *C*, corticotrophic stimulation test in adult singleton and twin sheep. The *y*-axis shows the decrease in ACTH AUC for every kilogram increase in birth weight. The numbers below the bars are the regression coefficients for birthweight in singletons (S), and the between twin-pair (β_B) and within twin-pair regression (β_W) coefficients for birth weight in twins. The effect size is largest, and statistically significant, for β_W, indicating that the decrease in ACTH AUC with increasing birth weight is due to factors intrinsic to each twin fetus, rather than to maternal factors affecting both fetuses.

not so distinct. The intrauterine environment is affected by two components: maternal factors (e.g. nutritional status, body habitus, ingestion of toxins), which will be common to both fetuses; and factors intrinsic to each fetus. Some of these fetal factors will be genetic, but others will not. For example, the proportion of the placental nutrient supply that each member of a monozygotic twin pair claims is not related to genotype. More recent studies have addressed this issue by including coefficients for both within twin-pair and between twin-pair factors in the statistical analyses, and these studies have tended to find the same associations between birth weight and risk of adult disease in twins.

The question of the effect of a twin pregnancy on outcome is not one that most animal experiments can address. The majority of the animal studies investigating the associations between intrauterine environment and long-term outcomes have been performed in polytocous species (those that give birth to several fetuses at once). Furthermore, these species often give birth to young that undergo critical aspects of organ development (such as of the pancreas) postnatally, rather than before birth as in the human. Clearly, if fetuses from multifetal pregnancies are fundamentally different from singleton fetuses, and long-term health is affected by stage of development at birth (as is now apparent in preterm humans), such species cannot be used to address these questions.

Altered developmental trajectory in twins may be determined in early pregnancy

The physiological reasons behind the altered fetal development, adverse pregnancy outcomes and long-term consequences for adult health that are associated with twin pregnancies are still poorly understood. The dogma is that reduced size at birth and gestational length in twins are related to an inability of the mother to adequately support more than one fetus to term: the competition between the twins for nutrients results in nutrient demand outstripping supply, and there is excessive stretch caused by two fetuses. These two factors then result in initiation of mechanisms that lead to preterm parturition. However, the fetus is known to be a highly effective nutritional parasite, and the signal transduction mechanisms initiated by uterine stretch do not appear to be advanced in multiple pregnancies. In fact, there is no evidence that twins are born earlier than singletons as a result of increased uterine stretch. Data from pregnancies in which the number of fetuses was reduced early in gestation (either spontaneously or through intervention) show a significant association between both gestation length and birth weight and the original number of fetuses, rather than the number that are actually delivered, raising the intriguing possibility that factors in early pregnancy, perhaps even around the time of conception, determine, at least in part, fetal growth trajectory and gestation length in twins.

Figure 2. Although twins may be discrepant in size (above), even the larger twin of a pair is, on average, smaller than the average singleton. Dizygotic twin pregnancies are also relatively common in sheep, with a similar reduction in birth weight distribution.

There is good evidence that periconceptional factors affect fetal development in animal studies. For example, we have demonstrated that moderate maternal undernutrition around the time of conception in singleton-bearing ewes (a principally monotocous species) leads to preterm birth and altered fetal development (Bloomfield *et al.* 2003). Maturation of the fetal hypothalamic pituitary adrenal axis (HPAA) and of the pancreas are advanced. In twin fetuses of well-nourished ewes, pancreatic development is also advanced compared with singletons (Fig. 1*A*; Rumball *et al.* 2008). However, other aspects of fetal development in twin fetuses, such as the fetal HPAA, are delayed compared with singletons (Fig. 1*B*). Ontological studies of HPAA maturation in sheep demonstrate, however, that both the accelerated development in singletons from undernourished ewes and the delayed development in twins are already present in mid-gestation and that placental glucocorticoid metabolism is also altered at this time. Intriguingly, in adult sheep born to periconceptionally undernourished ewes HPAA function is suppressed, whereas in adult twin sheep it is activated, and the degree of activation is related to the within-twin pair coefficient for birth weight (Fig. 1*C*). Thus, two different periconceptional events both have profound, but different, influences on fetal development that persist as altered physiology in adult life.

These experimental data are supported by increasing circumstantial evidence that gestation length and size at birth in human pregnancies are also associated with factors operating in the periconceptional period. For example, preterm birth in humans is associated with maternal undernutrition in early pregnancy (Rayco-Solon *et al.* 2005) and with exposure of the mother to severe stress such as an earthquake. Human studies also suggest that a discrepancy between actual fetal size and expected fetal size in the

first trimester predicts both small-for-gestational age and preterm birth (Smith, 2004). Male fetuses are already larger than female fetuses in early human pregnancy, and some twin studies have suggested that growth trajectories of twins diverge from those of singletons as early as 8 weeks gestation.

Do the periconceptional origins of the long-term consequences of being a twin matter?

The periconceptional period appears to be one critical period during which pregnancy outcome can be influenced. Adverse maternal exposures, such as undernutrition, and intrinsic fetal events, such as twin conception, both permanently alter the fetal developmental trajectory with consequences for post-natal physiology. The mechanisms mediating these effects are not yet known, but accumulating evidence suggests that epigenetic modification of DNA and histones may play a role and that epigenomic differences between members of monozygotic twin pairs may explain phenotypic differences (Poulsen *et al.* 2007).

The life-long consequences of periconceptional factors, whether they be the nutritional status of the mother or the presence of a co-twin, have implications for both research and for potential interventions. A conundrum for research design is whether fetuses from multitocous species are immune to developmental adaptations in response to additional (or fewer) fetuses, or whether adaptations similar to those demonstrated in monotocous species occur. Clearly, the answer to this question may impact on how findings in animal experiments may translate to the human situation. Further research into understanding the mechanisms and key signalling pathways that mediate signals from the periconceptional environment to the fetus, resulting in setting of developmental trajectory, is critical. Such research may lead to knowledge that could result in interventions before or during very early pregnancy which improve pregnancy outcome.

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Thinking the thoughts of a cell...

Austin Elliott caught up with Professor Sir Michael Berridge (below) in Manchester where he delivered the President's Lecture on 'Calcium signalling in health and disease' at the Summer 2008 EPHAR (Federation of European Pharmacological Societies) meeting

Professor Sir Michael Berridge FRS (right), well-known for his work on calcium (Ca) signalling and inositol phospholipids, was born in what is now Southern Rhodesia. He came to Cambridge as a PhD student and has worked for many years there and at Babraham.

Austin Elliott (AE) I wanted to start by asking a very long timescale question: do we know how far back in evolution Ca signals go, in primitive organisms?

Michael Berridge (MB) They don't seem to be present in bacteria as such, but they go back into fungi and plants. In plants it's quite interesting because they have all of the same elements that you see in mammalian cells. In addition to the temporal aspects that I was talking about today, and for example in root nodules, they can detect nod factors which are produced by fungi and soil. These act on cells in the root and they induce the formation of a nodule and to do that they induce these regular oscillations, absolutely beautiful, that go on for ages. So all the elements of Ca signalling are certainly well established in plants.

AE So both release of Ca from storage pools in the cell and stimulated Ca entry, they're there?

MB Yes, they are somewhat different because plant cells are dominated by the vacuole... so there are important differences [from animal cells]. But the basic principle of having an elevation of Ca, having strict control over the spatial and temporal aspects, is certainly well in place in plants. And, of course, it's present in insects and in worms such as *C. elegans*. There is some beautiful work going on Ca signalling in *C. elegans* and all the same elements are there as well.

AE One of the things that people who have been in Ca signalling... a while like to do is look [back] at the progression of the field and say: what were the key problems over the decades? You're famously associated with solving the problem of how Ca is released from storage pools, in the 1980s onwards, but you spent much of your lecture talking about spatio-temporal organization of signals in cells, which I guess is the 1990s until now. Do you think we've got wholly to the bottom of that problem, or is it still not quite solved?

MB I think we've got most of the elements. You can't divide channels up into smaller bits so we've now essentially got the basic building blocks. But I think we've just scratched the surface in most cell types. So there's still a lot to learn on how these systems are put together in specific cell types. And I really make a plea for looking at primary cells, because so much work now, in Ca and many other signalling pathways, is done in cloned cell lines. [That] work can certainly be helpful in identifying the components and studying how they might operate. But there's no escape from actually working on the primary cells. And there, I think, there is still an enormous amount of work to be done. We know a lot about cardiac cells, perhaps more than anything else. We know almost exactly, down to the number of channels occurring in the junctional zone. That sort of detail is absent in most other cell types. I think it's now just the long process of going into specific cell types and seeing how their systems are put together and how they work.

AE [That] fantastic level of detail that we've now got to in certain cell types [has] been dependent on the technical advances in how one measures these kinds of signals, which have been really dramatic. And of course you were there in the early stage of this in Cambridge in the late 1970s and early 1980s, when some of these ideas were just being booted around.

MB Yes, I remember quite distinctly, I started to try and grapple with this problem by developing Ca-sensitive electrodes, which turned out to be extremely difficult. And at that time, Roger Tsien was working with Tim Rink over in physiology and I can remember distinctly their coming over to ask me for advice on how to construct a Ca electrode. I think it was the only time I ever gave Roger Tsien any advice. And they arrived a few weeks later to ask some more questions and I'd already given up on Ca electrodes. I was starting to study phosphatidyl-inositol (PI) metabolism. They were absolutely appalled that I'd given up on Ca electrodes to study this wacky system of the PI response, but that turned out to be a wise decision. I think Roger gave up on electrodes and that's when he started looking at the indicators, and of course

it is extraordinary the kinds of indicators that he's produced. As you mentioned, it's what's fired the revolution really, going hand in hand with imaging technology. It's been extraordinary, what one can now see at the single cell level.

AE And of course, also in Cambridge, around the same era were Rex Dawson and Robin Irvine doing inositol lipid work. When I was [preparing for] this interview, I looked up the mission statement from the very first issue of the journal *Cell Calcium*, because it happened about this same sort of era. One of the things it [contained was] a summary of what was then vaguely known. And it said: "stimulated Ca entry in cells" and then it said in brackets "(coupled to phospholipid metabolism?)". And I remember this because it was the only question mark in the article. And at the time that was really, as you've mentioned, regarded by many people as a crazy idea. So what made you think... it was worth running with?

MB Well, I think really it was reading Bob Michell's review in 1975 or '76 (Mitchell, 1975). I really recommend to anybody, including young students, to read that review. It is an extraordinary, scholarly kind of review: he brought together biochemistry, pharmacology, physiology. But the main theme of the review, really, was the fact that, based on the pharmacology of many of these systems, some receptors were activating cyclic AMP, and not Ca. The other receptors were activating a phosphatidyl-inositol (PI) response. And [those receptors] were all activating Ca. So it was this association that he built up which convinced me that it was worth pursuing.

I then did some experiments, which would [take] a bit too long to relate, but the essence was that insect salivary glands were very permeable to inositol.

That was the way I was able to measure the PI response, by measuring the release of tritiated inositol from the glands upon stimulation. But then I realized that if they were losing this inositol, if I stimulated them hard and washed continuously, I might be able to deplete the lipid. That's exactly what happened and the Ca signalling then faded away. And then when I re-fed the cells with inositol the Ca signal came back again. And that absolutely convinced me that Michell was right, that there was a link between the two. And then one had to go on to try and find the link. But that really, in my mind, put [it] on a firmer footing, that this may well be what the PI response was about. But it was Michell's review that really got me interested.

AE You mentioned there the system that you were famous for many years for working on, which is the bluebottle salivary gland. Of course... invertebrate physiology has a classical place in physiology and pharmacology. But perhaps now, with the exception of niches such as *Drosophila,* it seems... less prevalent than it used to be. Do you think the use of systems [from] comparative physiology still has a place in the modern investigation?

MB *Drosophila* is still feeding... very interesting signalling molecules into the general arena. Like... Orai, a store-operated channel that emerged from screens done on *Drosophila.* The TRP channels emerged from *Drosophila* and there are many other signalling systems where *Drosophila* has actually been very important in feeding in information. The *Wnt* system is another example. The people in the *Drosophila* field are... very active and... very aware of the importance of their molecules with regard to mammalian systems. That's always at the end of [their] papers, as it were. So no, I don't think it's at an end. And *C. elegans* is coming on-stream now with [use of] genetic manipulation. That too is now feeding in important information

AE Do you think there's anything special we can learn from these evolutionary approaches? As more and more organisms are cloned, one gets to see these same mechanisms, as you've briefly alluded to, developing through evolutionary time, which is quite fascinating.

MB I think that's going to be quite difficult to handle, because the only way I can see that one might be able to do it is to really develop an understanding of, for example, muscle contraction. And it's hard enough trying to do it just in mammalian systems but one would then have to do it in a whole lot of other species. And then try and pick up what the subtle changes were. I'm not sure, at this stage, that it's worth the effort, to be honest. But in time it may well be.

AE Your lecture today was a tour through the way Ca signalling elements are 'selected' by different cell types and their differentiating programme to enable them to do their different jobs. One of the things that calcium scientists joke about after meetings is often: we know so much about this now, but relatively speaking, the amount of pharmacology it has so far generated is surprisingly small. We have the L-type calcium channel blockers, particularly for hypertension, but beyond that... sometimes people say: you might've expected more pharmacology. Do you think that's true? Or are we going to see more, do you suspect, in the next 10 or 20 years?

MB It's an interesting question. I think the problem is that the Ca signalling system is so central to everything the cell does, moment-to-moment. If you interfere with this too strongly, you really are in trouble. So it came as a great surprise when the voltage-gated channel blockers started to emerge. People were really surprised that the heart didn't stop, and so on. There seemed to be some degree of [tissue] selectivity and that may explain why they were so effective.

I think in time, if we really get to know and understand how the system is actually constructed, we might be able to start to develop more specific and selective drugs. But it will really be ways of subtly modulating the system. But when you think of how amazingly it's constructed in terms of these oscillations; they're very delicate beasts, these oscillatory systems. Minor tinkering and the whole thing could just collapse. So it's not an easy thing to do.

AE Yes, not an easy thing to modulate. The TRP channels, which were not in your lecture but have been the focus of much attention in the last 10 to 15 years, have been touted as one of the next generation drug targets. The rumours tell us that the drug companies are busy, but as yet there isn't much. Or at least nothing much that they're telling us.

MB I'll go back to this business of differentiation and studying specific cell types. It's hard to find an example of a primary cell which has a specific TRP function associated with it. The only one is Orai, which isn't a TRP channel, but is a store-operated channel. We know that Orai is very important in T cells. And we know that mutations in Orai lead to spontaneous SCID (Severe Combined Immunodeficiency). So there's a genetic mutation in a store-operated... channel, which is leading to a certain deficiency. That does suggest that something that would act on TRP channels, as you suggest, may well be an interesting target to deal with. But with all these other TRPs, it is really amazing that it is hard to tie down where they actually work in a specific process. There's plenty of information on cloned cells, but there's an enormous mismatch between all the work that's been done on these TRP channels, [and] relating that back to a specific cell type and saying 'the liver has TRP 6 and it's very important for doing *x, y* and *z*'. That part seems to be absent.

AE Well part of it is almost a Catch-22 because it's hard to probe the function without a selective inhibitor.

MB Yes, but the technology is there to do cell-specific knock outs and so on... but it's actually very difficult. The other thing which I think is so important is plasticity of the Ca signalling system. It has an extraordinary ability to be able to get around any imposed changes. Many of the knockout studies that have been done, it's just amazing how there's just an absence of a phenotype. But if you go in and look at what has happened, you find it's extraordinary, the way the cell has been able to go back into the toolkit, select out an alternative and put that in place, so that the cell looks quite normal. And it is this self-assessment mechanism that I mentioned. The cell seems to know, after it's differentiated, that it has to produce a certain type of calcium transient. And if you come in and suddenly pluck out one of [the] components, as long as it's got a certain amount of time, it can adapt in an extraordinary way.

These adaptations are not just replacing alternative components, they can actually adapt by changing, for example, the downstream effector systems. So people have been trying to knock out some of the N-type and R-type channels that promote exocytosis in synaptic endings. What they find is that... lo and behold, they actually start altering the profile of the synaptotagmins. [The cells] actually put in new synaptotagmins, which increased the selectivity of the

effector system. So even though the [Ca] signal is weaker, the end result is the same because you've got a more sensitive effector. Now to my mind that's the most extraordinary kind of adaptation. This relates back to your question about new drugs. You see you may be able to get something which dampens down *x*, but with time the cell will get around that and put something else in. And then you're back to square one.

AE At the end of your lecture [you talked about] the linkage of human diseases, and particularly of common diseases like diabetes and hypertension, to dysfunction in the Ca signalling toolkit. You were stressing not so much direct dysfunction of single elements, which perhaps is the way that we've been conditioned to think about it from genetic channel diseases, [the] channelopathies... but much more subtle aspects, to do with the regulation of whole panels of proteins. Could you tell us something more about that?

MB This is what I referred to as phenotypic remodelling and the question is: what drives that remodelling? It all comes back to the fact that this system has a plasticity built into it, which means that you can in fact bring about and actually accommodate subtle changes in the quality of the signal. And the question is: what's driving this?

For example, in hypertension you can trace from the fact that you have a high salt diet then this is going to impose an increase in blood pressure, and you will have water retention. That increase in pressure then feeds back on to the heart, which starts trying to force the heart to work harder so it now produces stronger signals. It achieves it's end, by increasing the force of contraction, but then you pay for that by the fact that the system is being unstable, it's not working at it's normal level. So then the cell tries to make adjustments to cope with this elevated calcium and then that leads to remodelling, which can have a catastrophic effect on the heart.

So it is a very subtle process, but I think the channelopathies are much simpler. You've got your mutation, you've got your change, in many cases these are lethal. [Other] mutations that we know about are those that aren't too serious, like the mutation in the Type I ryanodine receptor, which only shows up during anaesthesia [in malignant hyperthermia]...But these aren't the major diseases in man. The major diseases are these changes which occur in the phenotype [for example] through abuse. The system is desperately trying to accommodate [these changes], but in doing that it brings about other changes which finally have disastrous results. And one of the results is for example atrial arrhythmias [which are] due to phenotypic remodelling as well. These are the aspects we have to get to grips with and it's not easy.

You have got to understand the primary cell. That's the key point.

AE Yes, of course, with something like atrial arrhythmias, [one is] particularly perhaps thinking of stretch-induced ones, because many dysrhythmic problems result particularly from volume overload and stretch. And of course that comes back not only to primary cells but also to *in vivo* models, which is something else that both physiology and pharmacology have been coming back to, after 20 years of retreat.

MB Absolutely, I couldn't agree with you more.

AE You are well known as a very prolific and lucid review writer, from your original 1984 Nature review on inositol phosphates with Robin Irvine (Berridge & Irvine, 1984) onwards. With the proliferation of experimental papers in all fields, do you think reviews have become more important in that respect? One hears scientists repeatedly say that they struggle to keep up with the literature, so reviews provide a very important service to people.

MB I think they are very important. But there are reviews and there are *reviews*, of course! If they can be really objective then I think they serve an enormous value to the field and that's what I've always tried to do, to pull areas together and perhaps stick my neck out a little bit. There are times, when you immerse yourself in a field, you start to get a feel for what might be happening. You almost try to think like the cell thinks, as it were. And if you can write this down clearly and perhaps just provide a way forward. I've always advocated that but I know that there are lots of people who think that one shouldn't do this, you shouldn't be too speculative. But I've always thought that was the wrong way around. I think one should be speculative, because that's what we're about. We speculate when we start doing experiments. We speculate on how we think something works and then we do the experiments. There's no reason why you can't do that in other areas.

And that's what I've tried to do with my website (http://www.cellsignallingbiology.org), I've tried to summarise what I feel is the current state of different signalling systems in different cell types. That may suggest to some people new things to do.

AE One final question. There is a rumour that circulates in the field that you nearly didn't become a physiologist at all, you almost became a big game ecologist. Is that true, or is that just an urban legend?

MB No, that's true.

AE And this stems from your childhood?

MB Yes, I've been fascinated, since I was a child by African wildlife. I decided at school that I'd like to become a game ranger, but when I applied to the department towards the end of my school career they were a bit reluctant. They advised me to go into big game ecology because they thought that ecology was going to be the big thing in Africa. Of course they were right. But at that stage there was no ecology course as such. The only ecology courses in big game were run in California, and from the middle of Africa, that was a long way away. So I ended up going to do zoology, which was the closest that I got to that. I had a most amazing lecturer, Eina Bursell, a Danish insect physiologist [whose] lectures just blew me away – just extraordinarily interesting. In fact I remember to this day, he talked about the 'staircase phenomenon' in the heart. You had the beating heart and you applied [a hormone] and you got this gradual increase in the force of contraction. And I still remember that and being absolutely fascinated by this 'staircase phenomenon'.

Anyway, it's amazing that now, through my work on signalling, I now understand how that actually develops. It's really rewarding. But that's what took me away from the idea of being a big game ecologist. And that's what brought me to Cambridge to do a PhD with [Sir Vincent] Wigglesworth, on insect physiology.

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An extended audio podcast of this interview is on the British Pharmacological Society's meetings podcasts page: www.bps.ac.uk/site/cms/contentCategoryView.asp?category=357

Tomorrow's women, tomorrow's world

The Physiological Society, in collaboration with the UK Resource Centre for Women in Science, Engineering and Technology (SET), have set up a pilot mentoring scheme for women this year. As part of my role to aid the process of setting up this scheme, and to get a feel for the range of needs required by women I attended the conference held in March in London run by the UK Resource Centre for Women in SET entitled 'Tomorrow's women, tomorrow's world'. The conference and the mentoring scheme are not about women taking over the world but to help retain and recruit as many good female scientists as possible.

Currently women make up 33.5% of all higher education students in SET disciplines, and 25% of academics. As the level of seniority rises the percentage falls dramatically with only 8% of women professors. But where will we be in 2030?

In contrast to Physiological Society meetings, at this conference 97% of the delegates were female (as might be expected) with only two male speakers (The Minister of Science, Lord Drayson, and Philip Greenish). The audience was diverse with CEOs from major companies, academics, students, scientists/engineers from industry, women returning from career breaks and a Maths clown (who made a satellite out of balloons). The day was interesting and thought provoking as we considered where SET disciplines would be in 2030, that is 21 years time when my daughter of 10 months will be starting on her career ladder.

The day was chaired by Maggie Philbin of *Tomorrow's World* fame. She started the day off with an unscientific survey using her blog to ascertain the number of women in SET at senior levels. It showed that there were relatively few making the higher levels but Professor Walby (Professor in Sociology) stated that the statistics showed it was not education in schools that was the sticking point but further up the

Valerie Gladwell.

career ladder. Emily Cummins (an award-winning young engineer) refuted this point and believed that she was given incorrect advice at school, being persuaded against Maths and Engineering at A-level. Emily at 21 has already established herself as a well-known engineer with the development of a sustainable fridge (which is being used in Africa) despite having no formal education in engineering. She is an inspiring young lady and it is the young, bright individuals like herself that we need to educate and keep in SET disciplines.

Susie Uppal from The Equality and Human Rights Commission discussed the concrete ceiling effect that prevents women rising to the top, although sometimes it is the less visible constraints preventing women progressing. Their research suggests that pay widens in employees' early thirties, a potentially crucial point in young people's careers, but a time when some women's biological clock is ticking. This certainly is not the sole reason for the gap and efforts need to be made by employers (including those in Higher Education) to ensure that this gap narrows. Women can help themselves by networking both horizontally and vertically, Ayo Bakare from UK Resource Centre explained, as making useful contacts is crucial for progressing a career. This means that we should not just concentrate so hard on the tight-rope of our careers, desperately trying not to fall off, by only networking with people around us in similar situations but should strive hard to make links above ourselves (not just in our own organisations) and start climbing vertically up the rock face of our career path.

Professor Walby also discussed the economic downturn and how we should be prepared for recovery, with SET subjects high on the agenda to help improve the economy. We need to help maintain the UK as a main leader in research. Futurologist, Dr Shultz gave some fascinating insights into what we might be doing in 2030 including vertical urban greenhouses and meat grown in labs.

Annette Williams, the Director of the UK Resource Centre, gave her vision for 2030 which included the thought that 23% of professors in SET disciplines should be women by this time. We need to ensure women have the correct skills set to do this. As Maggie Philbin suggested, we should make sure that we all promote our strengths and our aspirations (women are particularly reluctant to do this) and seek help if we have weaknesses. This is where vertical networking may help.

So where do we go from here? How do we ensure we get more women at the helm of scientific excellence? As scientists, we need to engage the public and encourage parents to inspire their children, especially girls, to want to learn more about science. We need to give the correct advice to ensure that a sensible path is followed. For emerging scientists, we must have a good education system. I believe that The Physiological Society already plays a major role in this with its ambassador schemes and other outreach programmes.

If we wish to have more good female scientists we need to ensure that role models are visible, especially women scientists.

Just to test this: What famous female scientists can you name? Were they born in the 20th century?

The UK Resource Centre for Women in SET is an excellent wealth of networks, training grants and events, and links with public life positions (see www.ukrc4setwomen.org).

I am a Physiological Society Council Member, currently helping to set up the Physiological Mentoring Scheme for Women with fellow co-ordinator Daniela Riccardi and Elizabeth Bell.

Valerie Gladwell

The Society are pleased that our Mentoring Scheme has now made 10 matched mentor–mentee pairs for this year.

Profile: Emily Davies, participant on the BPS/Physiological Society *in vivo* short course

Eight years ago, the British Pharmacological Society and The Physiological Society set up *Short courses on in vivo pharmacology/physiology (*now known as *BPS/Physiological Society short courses on integrative pharmacology and physiology)* for undergraduate and postgraduate students in response to the decrease in the number of universities in the UK that offer *in vivo* training within their institutions. Funding for the courses, additional to that provided by BPS and The Physiological Society, comes from the Wellcome Trust, the BBSRC and the Pharmaceutical Industry and covers the cost of running the courses, student travel and accommodation expenses, attendance at a Home Office training course (modules 1–4), and the *in vivo* training course itself. Three courses are run each year, currently at King's College London, the University of Bristol and the University of Glasgow.

Emily Davies obtained a first class degree in Pharmacology from the University of Bristol and stayed on to study for her PhD in Physiology. The title of her PhD is: 'Developing somatosensory evoked potentials in vivo – a translational model for pain'. She attended the in vivo short course during her undergraduate degree.

How did you find out about the BPS/Physoc *in vivo* short courses?

I was informed about the course in a lecture during the 2nd year of my undergraduate degree at the University of Bristol. I was keen to participate as I was considering a career in research at the time and knew the course would provide me with invaluable skills. The course is organised and funded by BPS and The Physiological Society, and sponsored by a consortium of pharmaceutical companies, BBSRC and Wellcome Trust, and is therefore nationally recognised. A large proportion of biomedical undergraduate students do not get the chance to gain such skills and so it was a great opportunity.

When and where did you carry out your short course?

The week-long course took place in June 2007 at the University of Bristol, within the Department of Physiology and Pharmacology. Many different research laboratories within the University were involved. Prior to the summer course, I attended a 2 day Home Office Personal Licence training course and examination in order to hold a Personal Licence to carry out experiments under the Animals (Scientific Procedures) 1986 Act (ASPA).

Can you describe what the short course entails.

This intensive, specialised course involves a mixture of lectures, observation and hands-on experimentation, in order to gain an understanding of the physiological and pharmacological principles underlying *in vivo* experimentation. I was able to learn techniques such as small animal surgery, data acquisition and experimental design. Lectures were given by academia and industry representatives on the use of animals in biomedical research. During the course we were able to carry out and have input in our own experiments. Participants also had the opportunity to observe *in vivo* electrophysiological experiments in various labs within the University and get a taster of research life. Due to the large number of staff associated with the course, and the small student numbers, there was a great deal of expert guidance and instruction. Towards the end of the week there was a dinner which allowed us to socialise with principal investigators, post-docs and PhD students within the University.

Did the course reinforce your desire to do *in vivo* research as a career?

The course certainly provided me with many opportunities and confirmed my intentions to pursue a career in research. I decided to use my training and skills gained on the course to best advantage and I selected an *in vivo* final year undergraduate research project. This *in vivo* electrophysiological project gave me the opportunity to present work at international conferences including the triennial meeting of the International Association for the Study of Pain and the main meeting of The Physiological Society. I am now undertaking a PhD which also expands on the techniques I learnt. I believe my interest and enthusiasm in pursuing an *in vivo* research career in neuroscience has largely stemmed from the BPS/Physoc *in vivo* short course and the opportunities arising from it.

Why do you think that *in vivo* work is important in advancing biological science?

In vivo experiments are necessary in order to investigate whole system physiology and pharmacology and understand interactions between different body systems and their modification by drugs. This is not always possible using alternative methods in novel research.

How much of the course focused on ethics of animal experimentation and how important do you feel this is to someone planning a career in *in vivo* pharmacology?

Both the Home Office licence training course and the *in vivo* short course gave serious consideration of the ethics of animal experimentation. They emphasised the ethical

requirements under ASPA and the requirements of the University of Bristol. We were also taught about seeking and using alternative approaches and the importance of experimental design for *in vivo* research. I believe it is crucial for anyone embarking on an *in vivo* research career to have a comprehensive understanding of the legal framework relating to the use of animals in research and the ethical considerations.

How did the *in vivo* training course help you in choosing your PhD?

Gaining *in vivo* training at an early stage in my research career gave me the chance to continue *in vivo* research during my undergraduate degree and during this time I developed a keen interest in neuroscience, in particular pain research. This is the area of research I have now decided to pursue in my PhD.

How would you compare the value of the hands-on course with using computer simulations instead?

Computer simulations are particularly useful in reinforcing theory for undergraduate students but the hands-on course allowed me to put that theory into context. Although my undergraduate degree programme widely used alternative *in vitro* and computer-aided education methods, for individuals intending to undertake an *in vivo* research career it is important to learn the relevant skills in order to carry out productive research later in their careers.

Who do you think would benefit most from attending a short course?

I would definitely recommend the course to undergraduate students who are interested in a research career as I think it would benefit them the most, but also to postgraduate students wishing to gain new skills. There is a shortage of graduates with an education involving *in vivo* research, and in my case I found that potential supervisors when applying for my PhD really valued this training.

Where do you see yourself in 5 years time and what are your long-term career aims?

I would like to stay in academia and at the moment my career aim following my PhD is to take on a post-doc position and contribute original research to the field of neuroscience.

The courses are aimed at both undergraduates and postgraduates, with calls for nominations going out via Heads of Departments in the 4th quarter of the year preceding the course. For further details, please contact ks@bps.ac.uk or ebell@physoc.org

Judith Hall
British Pharmacological Society

Professor Tilli Tansey Inaugural Lecture

Models and mechanisms: aspects of biomedicine at UCL in the twentieth century, 9 March

A 'eureka' moment in the development of science is a beautiful thing to contemplate, and Tilli Tansey took her audience to such a time and place special for physiology: the perception that the signals passing between nerves may be chemical in nature. That the place was UCL and the development published within the pages of *The Journal of Physiology* sets the stage for Tilli's inaugural lecture that included numerous illustrations, several from the Society's archives.

Under her title 'Models and mechanisms: aspects of biomedicine at UCL in the twentieth century' she skillfully threaded together the interactions between clinicians, experimentalists, the pharmaceutical industry and the law, around her major theme 'The model molecule of the twentieth century' which 'we' now call adrenaline. Covering a century of 115 years, she encapsulated the synergy at work in UCL as a special place for Biomedicine (as it is now called) to florish beyond the strictures of anti-research medical pedagogues. As then so it is now, priority disputes and animal experimentation flag the need for continual exemplary practice.

Tilli Tansey.

Leading us through a talk peppered with lively anecdotes, we were privy to a treasure-chest of insights. How the wronged Bayliss countered anti-vivisectionists and sued them for libel – funding a scholarship in experimental biology. How UCL's Hill, and Beveridge of the London School of Economics formed the Academic Assistance Council, so important during the Nazi era (and sadly still vital) bringing, amongst them, Bernard Katz to A V Hill's group. How post-war physiologists gained from Fleming, whose 'valve' ('tube' to those across the pond) in many forms was available in ex-war department electrical equipment for the amplification of the nerve's electrical activity. Finally we were left to ponder which UCL scientist it was swaggering back to college from Tottenham Court Road with a gross of condoms tucked under his arm. One wonders how many were used as per the necessary chit, with the tips cut off.

Tilli is Professor of History of Modern Medical Sciences at UCL. She spent many years working as a neuroscientist before becoming a historian, specializing in twentieth-century medical sciences, especially physiology and pharmacology. Tilli has been The Physiological Society honorary archivist since 1990.

John Berriman

To listen to the podcast, go to: www.ucl.ac.uk/histmed/downloads/tansey_inaugural

Forty metre man leaves brain behind in Bristol

How The Physiological Society and Bristol Neuroscience celebrated the physiology of the brain this spring

Found: 1 brain, 4 m across, spotted in central Bristol on Friday 20 March 2009

Would suit 40 m man or woman

Does this brain belong to you or someone you know?

Contact: Bristol Neuroscience: bristol.ac.uk/neuroscience

Brain Awareness Week (BAW) – an annual international festival of neuroscience – was marked in Bristol this year thanks to a partnership between The Physiological Society and the University of Bristol's 'Bristol Neuroscience' (BN). With 70 BN neuroscientists, 15 from the University of the West of England, hundreds of children and thousands of members of the general public involved, the events run through this partnership gave a fantastic chance for Bristol's neuroscientists to share their interests with the wider community.

But how do you get people's attention to start with? Direct interaction and dialogue was at the heart of all BAW events, but they would have been doomed to failure if no-one was aware they were taking place.

Which is where a giant brain came in useful.

Giant brains and neurons with legs

As ways to raise brain awareness go, a giant brain, in central Bristol, surrounded by 400 'human neurons' was a pretty effective approach! It certainly didn't leave any doubts as to what BAW is about.

The role of the neurons was taken on by 5–11 year olds who had attended BAW school workshops, led by Lizzie Burns (sciencetolife.org), earlier in the year. Shoppers, tourists, office workers and commuters could not fail to miss the brain. People were encouraged to stop and discuss brain science with practising neuroscientists. The event also caught the attention of television, radio and press, extending BAW far beyond the brain's immediate audience.

Top, the giant brain was easy to spot in Bristol's busy Millennium Square; middle, EEG demonstrations: and below, looking at a model brain.

Neurobot , a model man showing how we detect and respond to touch and pain.

Exploring in Explore

After performing so brilliantly as nerve cells, all pupils had free entry to science centre 'Explore At-Bristol' where they could try out the BAW activities being run there throughout the week. Organised by neuroscientists from both Universities, these illustrated various aspects of brain science using, for example, a model man (neurobot) showing touch and pain, eyetrackers, and EEG.

Congratulations to the 100+ neuroscientists who survived the week (just!) supported by the University of Bristol's Centre for Public Engagement and At-Bristol staff.

And that's not all...

Alongside events described above, associated activities catered for other age groups:

Science cafés

Junior science cafés

Public lectures

Art exhibition

Finally, a huge thank you, in alphabetical order, to all project partners and funders:

Explore At-Bristol

BBSRC

Bristol Neuroscience at the University of Bristol

MRC

The Physiological Society (principal sponsor)

Quartet Community Foundation

RCUK

University of Bristol's Centre for Public Engagement

University of the West of England

For a full report, video footage, and photos, please see: http://tinyurl.com/bristol-baw

Anne Cooke
Bristol Neuroscience

The annual meeting of the Society for Gynaecologic Investigation

The 56th annual meeting of the Society for Gynaecologic Investigation took place on 17–21 March in Glasgow. The meeting was held next to the river Clyde in the Scottish Exhibition Conference Centre, the UK's largest conference centre, which includes a fabulous auditorium called the Armadillo. This meeting was a historic event because it was the first time that it has taken place outside of North America. The program included 150 oral communications and over 900 posters. There were also 15 mini symposia, including a fascinating session entitled 'Altered placental function as a cause of altered fetal growth' which was supported by *The Journal of Physiology*.

The Armadillo.

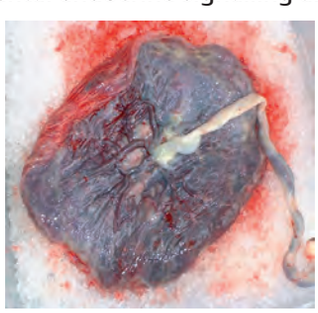
The placenta is the barrier between the mother and the fetus. It acts like a lung, a gut, a kidney and is a major endocrine organ regulating both the maternal and fetal biology. Placental function determines how effectively the available maternal nutrients are transferred to the fetus and therefore how well the fetus grows in the womb. Fetal growth is not just important in early life but also throughout life, as babies who grow poorly in the womb are more likely to develop chronic diseases including hypertension, heart disease, stroke and type-2 diabetes as adults.

Why bother understanding placental nutrient transfer was the question posed by Colin Sibley (University of Manchester) to start the session. Professor Sibley described the placental syncytiotrophoblast's role as a transporting epithelium and how it could respond to maternal and fetal signals to mediate the fetal nutrient supply. He also speculated as to how the placental phenotype could be used to provide biomarkers for fetal growth. His talk demonstrated how really important the placenta is.

Irene Cetin (University of Milan, Italy) then continued by discussing the importance of placental fat transport for fetal development. Diffusion and transport proteins mediate transport of the various fatty acids across the placenta, and this can be affected by both placental and fetal metabolism. Dr Cetin highlighted the importance of these processes not only in the normally growing fetus, but also in fetuses from diabetic and intrauterine growth restricted (IUGR) pregnancies.

'Is the placenta dying to get the baby delivered?' was a highly entertaining presentation by Michael Nelson (Washington University, USA); it is a unique ability to make IUGR and placental apoptosis humorous. I was intrigued by his description of the fibrin-covered clusters with apoptopic features that are present within the placental syncytiotrophoblast. The relationship between these clusters, hypoxia, apoptosis and IUGR was described using data from histology and cell culture studies.

Abigail Fowden (University of Cambridge) then concluded this session with an overview of placental endocrine signalling and how the fetus may signal to the placenta to optimize nutrient supply. If there is a mismatch between fetal nutrient supply and demand a signal such as altered nutrients, glucocorticoids or IGF's could lead to a change in placental phenotype to increase placental efficiency. Studies in the placenta may therefore be able to tell us about the fetal experience of gestation and may even be used to predict later health.



The human placenta.

The speakers.

The placenta was also the focus of one of the concurrent oral sessions of this meeting. This provided an opportunity for the new investigators to present their latest research which covered a range of topics from placental nutrient transport to trophoblast cell signalling pathways.

This meeting was indeed very informative and clearly demonstrated the importance of the placenta for fetal growth and the long term health of the baby. I am sure everyone who attended is extremely grateful to *The Journal of Physiology* for supporting this meeting.

Jane Cleal
Institute of Developmental Sciences, Southampton

Physiology News

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

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

Voice of Young Science Media workshop, March 2009

Breaking news: body absorbs 5lb of make-up chemicals a year. ***Reality***: scientists suggest cosmetics may have cocktail effect if absorbed into the blood stream.

How many of us have read a sensationalist headline in the media only to despair at the scientific inaccuracies being propagated to the public? Sense about Science is a charity which works with scientists to promote good science and evidence for the public, with the Voice of Young Science (VoYS) branch founded to aid early career researchers stand up for science in the public domain.

At a recent media workshop organised by VoYS, early career scientists were given the opportunity to form views on how science is portrayed and communicated in the media, and to directly question scientists and journalists on the 'frontline'. Representing the 'good guys', media-savvy scientists began the workshop with an unexpected defence of journalists, stressing the obligation of researchers to shoulder responsibility for the propagation of good science by clear presentation of the facts to journalists. Through the somewhat philosophical approach of Raymond Tallis, a former life scientist and novelist, and the enigmatic enthusiasm of Trevor Cox, media fellow for the Engineering and Physical Sciences Research Council, it became clear that it is possible to build a good relationship with the media and use its influence to the advantage of science.

One scientist who has experienced, first hand, the unfavourable exposure the media can bring, however, is Dominic Williams, senior lecturer at the MRC Centre for Drug Safety Science, whose research as a young scientist was thrust into the media spotlight due to an association with a 'hot' topic of public concern at the time. From this the audience raised concerns on dealing with contentious issues, to which all panellists emphasised the need for courage against being drawn into discussion on unrelated topics or difficult issues, and the importance of establishing in advance the 'agenda' or 'angle' to which the journalist is working.

The perspective of the 'bad guys' was put forward by a panel of broadcast and newspaper journalists, with local and national coverage. Presentations of the 'day in a life' of each journalist raised common themes emphasising the strict deadlines imposed upon science journalists, the lack of science specialists in journalism, and the impracticalities of fact checking and tracking down scientists directly involved in research detailed in press releases. When challenged by the audience concerning the 'sensationalist' reporting often seen by the scientist as responsible for turning science into 'pseudo-science', freelance journalist Judith Duffy explained the plight of the well-intentioned science journalist when writing any newspaper article. Science reporting is no exception to the rule and newspaper articles may be subject to cropping in the interest of space at the last minute, without consulting the author. More surprising was the revelation that it is not the author, but the next person up in the pecking order, the sub-editor, who is responsible for fitting the headlines to articles. This could be seen as journalists simply passing the blame; however, the comments revealed valuable information on the inner workings of journalism nonetheless.

Insight into broadcast journalism was provided by Rebekah Crabtree from the BBC, who urged the audience to consider their research or 'story' from the perspective of the average person on the street, someone she affectionately refers to as 'Sue'. Taking into consideration that the job of a journalist is to 'sell' a story (to both the editor and the reader), this is a tough job for a non-science specialist; it is not surprising to find that some of the facts may have been 'sexed up' a little. Rebekah highlights the difficulty journalists can have when interviewing scientists, and uses media-friendly scientist Trevor Cox as an example of a journalist's ideal science contact, explaining that a scientist who is good at digesting complex information into sound-bites understandable by 'Sue' not only makes her job easier, but helps avoid misinterpretation and preserve scientific integrity.

Finally, both journalists and media-relations professionals alike were keen to highlight the lack of early career scientists eager to speak up and get involved with the media. This was echoed in the final message of the workshop by Frank Swain, science writer and speaker, underlining the necessity of young scientists to be pro-active in assuming some public responsibility for improving the media profile of science and promoting good science.

Being given the opportunity to interact with both scientists and journalists at the VoYS workshop brought to the attention of those young scientists in attendance the necessity for a better dialogue and understanding between science and the media. The battle against 'pseudo-science' can only be won when we as scientists stop viewing the media as the enemy and learn to cooperate and use the power of the media to advance public understanding and uphold scientific integrity.

Ellen Forty
Faculty of Life Sciences, The University of Manchester

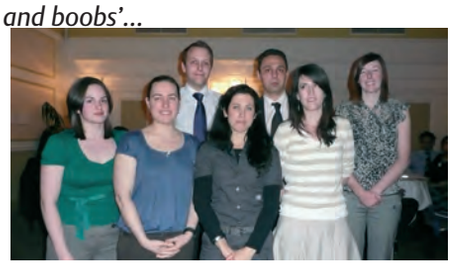
The Physiological Society is sponsoring these SAS workshops: part of the package includes a number of guaranteed places for Affiliates and younger Members to attend these very popular events. Opportunities to apply are advertised at regular intervals in our monthly email Newsletter. For further information please contact Liz Bell (ebell@physoc.org).

59th Annual Conference of the British Microcirculation Society Conference, 2009

Having last hosted the annual BMS meeting in 1997, the University of Birmingham was once again proud to welcome the 59th conference of the Society to its new and splendid Medical School facilities. Delegates were welcomed by Ian Booth, Dean of the Medical School, and the host Neena Kalia, who thanked them for making it the most well-attended and financially profitable meeting of the Society.

The host, Neena Kalia, welcomes delegates along with Gayle Halford, PhD student Ian Holyer and postdoc Dean Kavanagh.

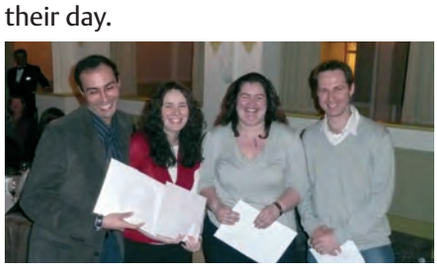
Jon Frampton (University of Birmingham) kick-started the designated symposium which this year was on '*Stem cells in the vasculature*'. His introduction provided an unbiased overview on the hype and reality of stem cell research for both the experts and non-experts. The hype was highlighted using tabloid articles, including one from the *Sun* (yes, that well known scientific journal we all aspire to publish in!), which only that day published a piece on how stem cells could be used to '*enhance bums and boobs*'...



7 of the 12 winners of the BMS student assistance travel awards – are girls better in science or is it just an un-representative photo!

Malcolm Reed, University of Sheffield, receives the BMS Clinical Lecture Award from BMS President Giovanni Mann and Andreas Gigler, Promocell.

When thinking of stem cells in the vasculature, endothelial progenitor cells immediately come to mind. Perhaps, therefore it was surprising to many to hear Petri Salven's (University of Helsinki) presentation in which he provided evidence that endothelial progenitor cells do not contribute to tumour neoangiogenesis, thus refuting data from over 50 published papers. The cat was set amongst the pigeons, but judging from the backlash, I would say the pigeons certainly had their day.



Winners of Promocell and BMS funded poster prizes and the Moor Instruments award for research conducted using novel technology.

Symposium speakers identified new regulatory factors impacting upon haematopoietic stem cell (HSC) trafficking, with Steffen Massberg (University of Munich) identifying an important role for platelets in guiding stem cells to sites of vessel injury. Tsvee Lapidot (Weismann Institute, Israel) illustrated the importance of integrating research from different disciplines by demonstrating how interactions between the nervous and immune systems regulated the role of HSCs in host defence and repair.

Birmingham's very own stem cell research featured extensively with symposium, free and poster communications from 10 of our finest senior and junior researchers. Phil Newsome (Consultant Hepatologist, University of Birmingham) emphasised that despite their clinical regenerative potential, adult stem cells could also contribute to the development of liver scarring/fibrosis – so not all that glistens (according to the *Sun*!) is gold.

In a move to increase the participation of clinical researchers at the BMS conferences, Malcolm Reed (Consultant Surgeon, University of Sheffield) was invited to give the BMS's inaugural clinical lecture. The current effectiveness of anti-angiogenic strategies for cancer treatment and future developments was discussed.

The Conference Banquet, held at the Birmingham Botanical Gardens and Glasshouses, was a huge success with the gently lit scenic gardens enjoyed by delegates, on what turned out to be a glorious evening (glorious for Brum in March anyway). Conversation flowed over a slow-roasted shoulder of lamb and good wine aplenty. Live Latin jazz music permeated the venue, quite loudly for some, leading to the inadvertent playing of Chinese Whispers around the dinner tables! By the end of the evening, the old victorian ballroom was once again buzzing with enthusiastic dancers – hopeless at salsa, though probably too 'under the influence' to realise.

I would like to use this opportunity to thank The Physiological Society for generously providing a Non-Society Symposium grant.

Neena Kalia

The Medical School, University of Birmingham

In the footsteps of giants

On my way to meet a friend in Hampstead, my attention was caught by an English Heritage blue plaque that carried the word 'physiologist'. I stopped to take a closer look and noted that the plaque commemorated Nobel prize winner Sir Henry Dale who lived at Mount Vernon House. A few months later whilst on a bus to work, I spotted another blue plaque commemorating statistician and geneticist, RA Fisher. Having been born in Hampstead myself, my curiosity was aroused as to how many other scientists had populated this leafy London 'village'. That an inordinate number of notable artists, actors, poets and novelists have called it home is widely known, but I decided to follow in the footsteps of its scientific giants, to see what else I could uncover.

Back to my initial discovery of the physiologist Sir Henry Dale, I am gratified to note that his blue plaque states physiologist, as his Wikipedia page refers to him as a pharmacologist (but then Wikipedia is not always known for its accuracy). Henry Hallett Dale was born in London in 1875 but his schooling and higher education (physiology and zoology) occurred in Cambridge. He went on to obtain a medical degree and moved to University College London where he worked under Ernest Starling. He is notable for proposing acetylcholine as a neurotransmitter, work for which he was awarded the Nobel Prize in Physiology or Medicine in 1936 jointly with his lifelong friend Otto Loewi. In addition to his many scholarly publications he wrote *Adventures in Physiology*, which was published in 1953. A review of this book by Marthe Vogt can be found in *Experimental Physiology* (Vogt, 1953). Sir Henry died in Cambridge in 1968.

If you have ever wondered why the test statistic for the analysis of variance is F, the answer is because of Sir Ronald Aylmer Fisher, who developed it. Born in London in 1890, Fisher's childhood was spent in a very comfortable house in Hampstead. He was a precocious mathematician and obtained a first in Mathematics from Cambridge in 1922. He became interested in genetics and also in eugenics, co-founding the University of Cambridge Eugenics

Society and he succeeded Karl Pearson as Galton Professor of Eugenics at University College London in 1933. He became friends with Charles Darwin's son Leonard, then President of the Eugenics Education Society. The study of eugenics flourished during the first half of the 20th century, when Fisher was a young man, but it lost popularity with the rise of Nazism. Fisher returned to Cambridge as Professor of Genetics in 1943. He published prolifically on both genetics and statistics and died in Adelaide in 1962.

RA Fisher's intellectual differences with his predecessor at University College, generated personal enmity towards his fellow 'Hampsteadian', to the extent that he would not publish in the leading statistics journal, Pearson's *Biometrika*. The blue plaque that commemorates Karl Pearson in Well Road, Hampstead, describes him as a pioneer statistician. Born in 1857 in London, he was educated at University College School and studied Mathematics at Cambridge, where he graduated as Third Wrangler in 1879. He then studied Physics in Heidelberg, Germany and moved on to the University of Berlin where he attended the lectures on Darwinism by the physiologist Emil du Bois-Reymond. Back in London he was introduced to Charles Darwin's cousin Francis Galton, the pioneer of eugenics who became something of a hero to him. When Galton died in 1911, he apportioned a part of his estate to establish a Chair of Eugenics at University College London and Pearson became its first holder. Karl Pearson was indeed a pioneer of statistics; he was instrumental in developing linear regression and correlation and the latter test which bears his name, was the first important effect size to be introduced into statistics. He formulated the chi-square test and classified probability distributions that formed the basis of much of modern statistical theory. Unlike his scientific neighbours above, Pearson refused the knighthood he was offered in 1935. He died in 1936.

In a house in Bracknell Gardens two generations of Huxleys are immortalised by a blue plaque, Leonard Huxley, son of 'Darwin's bulldog' the zoologist Thomas Henry Huxley, and his own sons Julian and Aldous. Leonard was a schoolteacher and writer, notably author of Charles Darwin's and other biographies. His son Aldous, also a writer, is probably best known as the author of Brave New World, reported to have been influenced by his brother Julian's occupation as a biologist. The Huxleys of Hampstead are members of the distinguished Huxley family, which includes the younger Huxleys' half brother, physiologist Andrew Huxley. Julian was an important proponent of natural selection at a time when Darwin's ideas were refuted as scandalous. Born in 1887, he graduated in zoology from Oxford. He was a keen ornithologist, and studied avian courtship behaviour during his early career. In 1912 he moved to Texas, USA, but returned to Oxford in 1916 to take up a Fellowship in the Department of Zoology. This was followed by a move to King's College London where he took up a Chair in Zoology. He was a co-founder of the World Wildlife Fund and the first Director-General of UNESCO. Prior to the Second World War, Julian was a prominent member of the British Eugenics Society and its President from 1959–1962. A committed humanist, he later revised his views and came to believe that race was a meaningless concept in biology. He died in 1975.

It might appear from my account that early 20th century Hampstead was a hotbed of extreme right-wing idealists, but it must be noted that eugenics was not viewed in the same light then, as it is in the post-Nazi era.

As an aside, and to complete my tour, I had often wondered why the road leading to the Hampstead campus of UCL Medical School is called Rowland Hill Street and once again the answer is on the blue plaque – it's named after Sir Rowland Hill, the originator of the Penny Post.

Patricia de Winter
University College London

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Aspiringate

It happens every Monday at around 9am. I become paranoid and agitated and feel that I am being watched by an unseen evil force. Actually it's my head of department. This Monday the paranoia was far worse as over the weekend I became embroiled in a global physiological and pharmaceutical conspiracy. A health professional with a physiology degree ('I've got a 1st' she kept saying) approached me and announced that 'big pharma' and the media were engaged in a conspiracy to make huge amounts of money out of her patients and the British taxpayer. As I am a fan of disturbed conspiracy theories I asked her for some detailed scientific evidence. The evidence was in fact deeply disturbing. A number of scientific papers and magazine articles had suggested that half a soluble Aspirin a day was beneficial for a wide range of ailments including protection from heart attacks and strokes. But! She had realised that because of the recent failure of a range of blockbuster drugs, the 'devious bastards' in the 'neocon controlled western drug industry' were attempting to shore up their profit margins by brainwashing the entire British public into taking half an Aspirin a day. 'They really are evil; that's exactly what they did with anti-AIDS drugs in Africa.'

She was going to warn her patients and inform them about a natural alternative that they could acquire easily from the health food shop.

'I am sure we can put a stop to this', I said; 'there are a number of unusual channels we can use'.

After consulting the dark and hidden corners of the internet where traumatised victims of the ruling elite communicate and share their pain (Lee Harvey-Oswald, Sirhan Sirhan, James Earl Ray, Princess Diana and Sarah Palin all use one site). I decided to expose their evil wrongdoings by writing a letter.

Dear Big Pharma,

Recently I was approached in an underground car park by an informant who for security reasons I will call 'Reg'. OK the informant was a woman, wasn't called Reg and it was a hospital, but in 1976 I watched Deep Throat talk to Bernstein and Woodward in *All The Presidents Men* and I suffer from serious psychological flaws. I thought that by placing my actions into an important historical context it might inflate my ego and sense of self importance.

And I ramble.

But! She has provided me with conclusive evidence that you are engaging in a conspiracy to brainwash the British public into thinking that consuming half an Aspirin a day will prevent heart attacks and strokes. I believe you to be criminal masterminds but would like to suggest a couple of minor caveats that you need to consider before you go on a conspiratorial rampage.

Just look at this conspiracy from a three stage logical point of view.

Firstly. Recently I bought 16 Aspirin from Tesco's for 16p (as you had cunningly forced the Chief Executive of Tesco to put them on special offer) this means that when you brainwash me to take half a tablet a day for 365 days a year, you could possibly fleece me of nearly £1.83 per annum.

Secondly. There are approximately 60 million people living in the UK, if you exclude small children, people with stomach ulcers and the emotionally delicate (people who think the government is controlled by aliens, health food fanatics, vegans etc.) from this total you could end up with around 50 million customers. 50 million multiplied by £1.83 comes to £91.5 million.

And finally. Pharmaceutical sales in the UK in 2008 amounted to over £10 billion.

I am usually quite polite but as conspiracies go this one sucks. You are conspiratorial neophytes and a bit dim. 91 million quid is not going to go very far in the pharmaceutical industry is it. That's £91 million even before you have deducted the cost of bribing a range of government officials and journalists at the BBC. Being a naive innocent boy I don't know what the going rate for corrupting the influential is, but using recent events in the banking crisis by way of a comparison it's not going to be cheap.

As an alternative I would like to offer my services to you as a conspiracies consultant: you have, for instance, been particularly slow in the growing field of 'natural' blood thinners. Recently I looked at a packet of a natural blood thinning product in a health food shop. 50 days' supply cost £6.50. By brainwashing the public into taking these instead of Aspirin you could fleece an individual for nearly £47.50 a year. Multiply that by 50 million potential victims you end up with £2.36 billion. Now that's money worth defrauding. And the whole beauty of this con is that when a medicine has absolutely no physiological effects, you get two additional competitive advantages: you don't need animal testing and you never get adverse reactions.

Another thing I could advise you with is a technique I have developed called 'guilt motivated neurolinguistic programming for marketing undesirable substances' (best destroy any paperwork relating to this one). Using this technique you can exploit the understandable sympathy that people have for indigenous aboriginal populations in the developing world. In essence, we invent a tribe of endangered Amazonian hunter gatherers 'the Fukawi', claim that they all live to at least 100 years in age and suggest that research demonstrates that they are immune from heart attacks and strokes. Then comes the 'sting'; we paint a picture of an Amazonian hunter on the packet and suggest that 50p per packet will be donated to the Cormorant Foundation (a charity founded by the distinguished philanthropist Keith Cormorant to protect the rainforests). The beauty of this little conspiracy is that the Fukawi don't actually exist and the Cormorant Foundation can be used to siphon 50p per packet (tax free, minus 12.5% handling fee) into your own personal offshore banking account. If by chance some curious anthropologist ever decides to go looking for the Fukawi, we claim that they have been exterminated by global warming and an uncaring capitalist society (thus making us look ecologically responsible and caring). Similar techniques have been tried and tested to destruction in the banking sector over the last 10 years and I am supremely confident that we can get away with such a scheme with no danger of any criminal complications.

If this initial conspiracy is successful there are a number of other conspiracies where I could offer my valuable services. The Nelson Mandela Homeopathic Prion Busting Kit is just one of a number of products that we could co-develop to fleece the general public.

And just one more thing, you really do need to silence the informant.

Sincerely yours

Dr Keith Cormorant

PS Seriously, for a minute, the first part of the article is highly accurate. The real scary thing is that 'Reg' is actually allowed near real patients.

Open access does more harm than good when based on a 'pay to publish' business model

The traditional business model adopted by publishers of scholarly journals, that we may call 'publish for free and pay to read', leads to an inevitable disparity in access to scholarly literature. The rising costs of journals and the shrinking budgets of libraries have only served to exacerbate this disparity. Admittedly, the open access movement has done a great deal to create a near level playing field for readers of scholarly literature. But I would argue that the segment of open access publishing, that depends on a business model that we might dub 'pay to publish and read for free', does more harm than good.

Authors by no means have a level playing field even in the traditional publishing model. The complex dynamics of peer review makes it difficult, if not impossible, to ensure that publication of an article is merely a function of its quality and is not influenced by such extraneous factors as the modishness of the topic, the name of the author or even the address of the author. The 'pay to publish and read for free' model adds a significant new dimension to the unevenness of the playing field for authors. It is often pointed out that page charges are waived for authors who cannot afford to pay. But it is hard to believe that a business model which depends on payment by authors can afford more than a marginal number of such waivers. Besides, why should anyone want to live on charity? One has also heard the argument that it is not really the author but the granting agency that funds the research that actually pays. This argument does not wash well either; if anything the playing field is even more uneven for getting grants. More importantly, this will undermine rather than encourage the whole genre of grant-free research.

The new exacerbated uneven playing field for authors (the old problems associated with the peer review have by no means gone away) will be disastrous for the underdeveloped world. It is often said that we are increasingly living in a knowledge economy and that while we may never have equality among the world's nations in military or economic power, knowledge is one area in which we can hope for true equality. If there is any truth in all of this, a 'read for free and pay to publish' model would indeed be disastrous for the underdeveloped world as it would encourage its citizens to remain consumers (readers) of knowledge rather than become producers (authors) of knowledge – a form of knowledge slavery.

If I have to choose between the two evils, I will certainly prefer the 'publish for free and pay to read' model over the 'pay to publish and read for free' model. If I am really forced to choose between publish or read, I would surely choose to publish. Who would not? Fortunately, there is growing evidence that a 'publish for free and read for free' model can indeed be made viable. Journals published by the Indian Academy of Sciences (www.ias.ac.in) and Medknow Publication and Media Pvt. (www.medknow.com), are just two of many examples. I believe that we just need to keep up the pressure on those who continue to adopt the 'read for free' model only at the cost of 'pay to publish'. At the very least we must prevent publishing in such journals from becoming too fashionable and/or mandatory for career advancement.

A previous abridged version of this piece published in *Nature* (Gadagkar, 2008) was misunderstood by some, probably because of the somewhat misleading title used by *Nature*[1] (Sandal, 2008) but thankfully not everyone appears to have misunderstood me[2](Brimblecombe & Sturges, 2009). I certainly have no quarrel with the large segment of open access publishing – those journals and other open archive efforts that are attempting to enhance the 'read for free' content without making the authors pay – indeed I welcome them all. My quarrel is only with that segment of open access publishing which makes 'read for free' possible only at the expense of 'publish for free'.

I thank Gesine Bottomley, Chief Librarian, Wissenschaftskolleg zu Berlin, Peter Suber, Research Professor of Philosophy at Earlham College and Catriona MacCallum, Senior Editor of *PLOS Biology* for many helpful discussions, but hasten to add that this is not to imply that they necessarily agree with all that I have said. I also thank the Wissenschaftskolleg zu Berlin for providing an intellectually free and liberating atmosphere.

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Physiology curriculum for medical training

The joint Physiological Society/ BPS Medical Training Working Group has been working with Richard Dyball to produce a core Physiology Curriculum for Medical Training. A draft is now available for comment (http://www.physoc.org/site/cms/contentChapterView.asp?chapter=139) and will be presented for discussion at the forthcoming Teaching SIG Workshop at our Main Meeting in Dublin. For more information please contact Liz Bell (ebell@physoc.org)

Animal research in medicine: 100 years of politics, protest and progress

The Story of the Research Defence Society. By John Illman (2008). Research Defence Society, London. £9.95

ISBN 978-0-9560008-0-4

For anyone doing public engagement on the subject, or even with an interest in it, this book provides a perfect overview of all the basic things that are useful to know as researchers about the broad topic of animal research. In a climate where communication of our work is so important, this book makes a comprehensive easy read covering the facts and figures which are useful in a debate about the use of animals in research.

This book really does follow the 'what it says on the tin' policy. John Illman does exactly what the title says in telling the story of the Research Defence Society (RDS) since it was formed as the Association for the Advancement of Medicine by Research (AMMR) in 1882. By describing, in digestible detail, the history of research over the past 2 centuries, Illman talks through the changes in opinion on the subject of animal research since the very beginning. The book begins with some history, outlining early animal experiments and also some of the first anti-vivisectionist movements, followed by the set up of the AMMR to counteract them. He talks of the success of anti-vivisection groups and of animal rights terrorism on public opinions of research in the past. A very interesting aspect is the description of how the laws have changed through history to the benefit of animals and researchers. The book, although only 72 pages long, is brimming with fascinating facts, not only about the animal research itself, but social issues over the years including political aspects. The last few chapters of the book show how, in recent years, the tables have turned. Media headlines started to appear on the side of researchers. Public engagement about the benefits of animal research, and more open policies about work from scientists, with the support of the RDS and others have started to impact on opinions and help people to understand why animal research is necessary – a true sign of progress.

Fiona Randall

Essentials of ecology

By C R Townsend, M Begon & J L Harper (2008), 3rd edition. Blackwell Publishing, Oxford. £29.99

ISBN 978-1-4051-5658-5

This is the third edition of a well-established introductory text. It is designed to be used by students undertaking a beginners' course and to be a succinct treatment of the subject. In these objectives previous editions were successful, so how could the authors have improved on the previous text? They have managed to do so by a number of innovative changes designed to make the text even more usable than before. Each chapter now sets out the key concepts to be addressed; marginal annotations provide succinct signposts of content almost paragraph by paragraph; each chapter concludes with a set of review questions; and boxed text usefully considers selected topics in depth under the headings of 'Historical landmarks', 'Quantitative aspects' and 'Topical ECOncerns'. Additionally, the book's evolutionary focus, a strength of this text, has been extended by a new chapter on evolutionary ecology, which provides additional material on molecular ecology.

Also, this text has always been characterized by its readability. For example, the complexity of arguments about the meaning and evidence for community stability is explored with remarkable clarity. This is not an isolated example – there are plenty of other difficult areas treated in a similarly exemplary manner. Throughout, the authors have avoided over-simplification and retained explicit links to the primary literature; indeed, many new studies have been added in this edition. These frequently incorporate substantive tables and informative figures with outstanding artwork. One quibble, however, is that the referencing is not consistent. Some figures have citations for the source, whereas for some the citations are in the accompanying text. This occasionally produces confusion as to the source of the study. Similar inconsistency is also found in the companion website where the tables have sources cited but the figures do not. This is regrettable for the authors are to be commended on continuing to provide such an extensive evidence base.

The companion website is, by current standards, somewhat limited, although doubtless it will develop. Multiple-choice questions are provided for self-testing, but these are relatively unsophisticated in structure. The authors could benefit from some technical advice on constructing such tests. One useful addition to the companion website would be some example responses to the 'challenge questions' of the review questions sections. These 'challenge questions' are discursive in nature and it would be helpful to the reader to have some indication of how the authors might have approached these. The other review questions are primarily concerned with each chapter's factual content and indeed should not have the answers supplied.

In summary, the authors have undoubtedly added to the utility of this text. It is extremely easy to locate any particular topic as required, and the pedagogical features added help to make the content accessible and understandable. A rather nice feature is that the different sections of the book are colour-coded so that they can be identified with the book closed. However, I suspect that the pastel colours employed to do this may become indistinguishable in a well-thumbed copy. And there is no doubt that owners of this text will use it a lot.

Glenn Baggott

A thinking approach to physiology

By Ian Sabir and Juliet Usher-Smith, World Scientific Publishing Co. Inc. pp. 232, £25.00

ISBN 9789812706027

The title of this slender volume rather belies its contents; I would describe it as a physiology primer. If taken as such, one's expectations are more accurately met. The book is divided into seven chapters covering the physiology of the major systems in the human. The main problem is that it is not specialised enough to adequately serve the needs of undergraduates in physiology; it is rather prescriptive and there is minimal emphasis on experimental evidence.

Throughout the book, text in grey boxes highlights clinical conditions associated with malfunction, and suggests that it was written primarily as an introductory text for students of medicine.

The Introduction is extremely brief, providing a skeleton overview of units and normal values commonly used in medicine. I think I would prefer normal ranges to normal values, or at least a statement that the values are approximate and vary. The seven chapters cover the electrical properties of cells, muscle, the digestive, respiratory, and circulatory systems, the kidney, and lastly integrative physiology. I became irritated when on page 2, I noticed that 'lose' and 'losing' were misspelt as 'loose' and 'loosing'. This immediately put me on my guard for further spelling or grammatical errors of which I found not a few.

The first two chapters deal with the properties of excitable cells and cover the resting membrane potential, ion channels, the nerve action potential and its propagation, synapses and the neuromuscular junction, myelinated and unmyelinated axons, the three types of muscle, excitation–contraction coupling, and intracellular calcium regulation. The level is very superficial and the purpose of some of the figures is unclear, for example, Figure 23.

Chapter 3 covers the digestive system and is relatively straightforward. The overall structure is described, motility is briefly discussed, and digestion of the major food groups is very briefly reviewed as is the endocrine control of digestion. Again, the purpose of some of the figures is puzzling, for example, Figure 37, the emulsification of fats by bile salts. The fourth chapter deals with the respiratory system. The first half of the chapter deals with the mechanics of respiration. In the latter half of the chapter, the section concerned with gas exchange contains some serious errors. The equation given for Fick's law is incorrect, as is that for the diffusion coefficient. Gas exchange is driven by a difference in partial pressure and not concentration as implied by the authors. It makes a simple story to say that CO_2 diffuses 23 times faster than O_2 but it is not helpful, as is done here, to confuse the rate of mass transfer with the rate of diffusion, as quantified by the physical diffusion coefficient. The remainder of this chapter discusses transport of oxygen and again oversimplifies to the point of error; for example, the authors describe a shift in the oxygen–haemoglobin dissociation curve to the right as a Bohr effect, which, although not totally incorrect, fails to indicate that Bohr shifts leftward can also occur. The fifth chapter is concerned with the circulatory system and haemodynamics. This chapter is, on the whole, more accurate and the figures are more pertinent than those of the preceding chapters. Flow, the cardiac cycle, cardiac output, venous return and the Starling filtration–reabsorption mechanism are discussed.

The penultimate chapter is concerned with the kidney. I think the thing that irritated me most was the constant use of 'filtration' in place of 'ultrafiltration'. Urine is filtered under high pressure, thereby the process is ultrafiltration. This is a shame because the chapter was otherwise a reasonable summary of renal function, although I would like to have seen a little more here on the kidney's function in the maintenance of blood pressure.

I liked the concept of a final chapter that deals with the interactions of different physiological systems in the body. This chapter, entitled 'Integrative Physiology', explored the control of plasma pH, control of arterial blood pressure and the response to exercise. It is regrettably short and the book would have benefited from expansion of this chapter. The paperback version of this book retails at £25 and I think I would recommend that physiology students put the money towards a more definitive text and give this one a miss.

Patricia de Winter

Max Perutz and the secret of life

A biography by Georgina Ferry. Random House, pp. 352, £25

ISBN 9780701176952

Max Perutz was one of my scientific heroes. More than half a century ago, as a final-year physics undergraduate in Oxford, I read about the just-published DNA structure and asked my tutor about the possibilities of applying physics to biology. My tutor, the physicist Francis Price, said that he personally knew little about the field, but he 'believed there was a very good man called Max Perutz in Cambridge' who did such things, and that I should write to him. I always suspected that Francis, who had been a scientific 'boffin' during the war, had come across Max in a similar role. Shortly thereafter, however, I noticed a job advertised at King's College London, at the other end of the DNA axis, and applying there I was appointed to JT Randall's laboratory. I have often wondered how things might have panned out had I not seen the King's advert and instead had followed Francis' advice.

As it happened, then, I never did work with Max Perutz, but I met and talked to him often at scientific meetings, read many of his papers, and went to hear him speak whenever I could. He was always ready to listen to different ideas and viewpoints and was unfailingly gentle and courteous in discussion. It was therefore a pleasure to read this biography, which brought alive the man himself, from his school days in post Austro-Hungarian Vienna to his long association with the famous Laboratory of Molecular Biology (LMB) in Cambridge.

Georgina Ferry had already written a splendid biography of Dorothy Hodgkin (another of my scientific heroes) when she was asked to meet Max on his

death-bed and agreed to write this book. Working from accumulated letters and papers, and from interviews with Max's friends and colleagues, she has given us a very valuable portrait of Max and a vivid account of his life.

Born in 1914, Max was already working in Cambridge at the outbreak of the war and was interned as an enemy alien, first on the Isle of Man and later in Canada. This much I had known, but the details of the military foul-up that constituted the internment process surprised me. We were lucky that Max was not lost to UK science, either to US academe or on the Atlantic to a passing U-boat. Later, released after the efforts of friends and colleagues, he worked on the Habakkuk project, a Churchillian enthusiasm for possible floating airfields of ice for which Max's Austrian skiing and mountain-ice experiences were ideal. The project is also covered in the biographies of Solly Zuckerman and Desmond (JD) Bernal (more heroes!) but the detail given here is fascinating. As a one-time National Service Junior Officer, I could readily visualize Louis Mountbatten drawing his revolver at a demonstration in Canada to illustrate the resilience of the modified ice that Max and his team had produced – and narrowly failing to wound himself and an American Admiral with bullet ricochets.

The long struggle that Max had to understand the structure and the molecular operation of haemoglobin, with its victories and setbacks, is very well described; Ferry has a talent for making complicated scientific concepts vivid and clear. Max was awarded the 1962 Nobel Prize for Chemistry for this work, jointly with John Kendrew for myoglobin. That was also the UK's scientific '*annus mirabilis*' when Watson, Crick and Wilkins were awarded the Medicine and Physiology prize for DNA. All five are pictured before the Nobel banquet together with the Laureate for Literature, John Steinbeck. Steinbeck was obviously no scientist, but coincidentally is the author of one of the best literary portrayals of a practical scientist, 'Doc' in *Cannery Row*.

Historical vignettes occur throughout the book. Despite his scientific distinctions, Max was not made an Honorary Fellow of Peterhouse until after he was a Nobel Laureate. Was this English suspicion of someone from a different background, one wonders? Again, it was interesting to read further on that even a Prince Nobel of science could have his paper to a leading journal rejected because of a single catty comment by an ignorant and anonymous referee; I had supposed that this treatment was reserved for lesser mortals like myself – or perhaps I could allude to TS Eliot's Prufrock and call those of us below the Princes 'attendant Lords'!

An outstanding achievement of Max's career was the establishment of the LMB, which was set up by the MRC under Max as an unobtrusive chairman rather than as titular Director. This was not their usual modus operandi, but it was his own idea. He succeeded in running the Laboratory, encouraging and facilitating first-class science and keeping an array of scientific prima donnas happy, all with a light touch and without a large number of boring 'administrative' meetings. Would that all departmental chairmen had the character and conviction to do likewise. It was probably in the same vein that he rejected the offer of a knighthood, because the title would tend to set him apart from his laboratory peers. It is good that he later accepted an appointment to the much more distinguished Order of Merit.

Max continued to do good science until he died from cancer in 2002. He also continued to write about science itself, sometimes targeted for laymen; this was another side of his multifaceted scientific genius. I highly commend Ferry's book to anyone who is interested in the life of one of the great scientific gentlemen.

I had intended to close this review by posing the problem of who in fact reads scientific biographies, even ones as excellent as this. While I was reading the book I was upstaged by Georgina Ferry herself, in a very perceptive article in *Nature* ('A scientist's life for me'; *Nature* 2008, **455**, 871–872). She begins by quoting Peter Medawar's remark that 'the lives of academics, considered as Lives, almost always make dull reading'. The article is well worth a read; Ferry surveys the field and its problems very well and it would be superfluous to do so again.

For myself, I remember reading CP Snow's novel *The Search* (about scientific fraud, but probably with some factual background in his own experience) before I read Jim Watson's justly famous *The Double Helix*. Both read as detective stories (as Crick remarked about Watson's book), so perhaps this 'detective element' is the essence of successful scientific biography. It is not easy to achieve this, though, and more often than not we are left with the style of Royal Society or National Academy of Science obituaries – worthy accounts of the science but with the personality of the scientist not very apparent. I hasten to add that this is not true of Georgina Ferry's biographies of Hodgkin or Perutz, either – or both – of which would grace the bookshelf of anyone interested in the greats of 20th century British biological science.

Gerald Elliott

Membrane transport in flux: the ambiguous interface between channels and pumps

Philosophical Transactions of The Royal Society B Biological Sciences. Vol 364, No. 1514. pp. 143–276.

The publication reports on a Royal Society Discussion Meeting held in 2008, that focused on the overlap in function between channels and transporters. Proteins are present in cell membranes to facilitate the flux of ions and a variety of other molecules across the cell membrane. Given the central role that trans-membrane flux of molecules has on the normal functioning of all cells, these proteins are a subject of intensive study. Of particular interest is the pathology that can result from the malfunction of these proteins.

These membrane proteins have traditionally been divided into two separate classes: ion channels and membrane transporters of which the voltage gated sodium channel and the sodium pump, respectively, are two well-known examples. The distinction between these two classes are that the ion channels are pores in the membrane across which ions move down their electrochemical gradient, whereas transporters have

a more complex mechanism where substrates bind to the transporter with the resulting conformational change in the protein resulting in translocation of the substrate across the membrane followed by release from the transporter. There is accumulating evidence that such rigid distinctions between the two classes of membrane proteins must be reassessed. It is known that the class of sodium-coupled amino acid transporters can conduct small ions in the presence of the substrate, thus it appears to function as both a channel and a transporter. It is hypothesized that membrane transporters may have evolved into channels via the loss of a gating mechanism, and more tenuously that channels may have evolved into transporters by the addition of gating mechanisms.

In this volume leading researchers in the field focus on examples of membrane transport proteins (ABC proteins, neurotransmitter transporters, CLC proteins and the sodium pump) that most clearly illustrate the 'ambiguous interface' between channels and transporters.

Angus Brown

At a glance

The Wiley-Blackwell *At a glance* series for medical students breaks complex subjects into short, easily digested topics. Each topic is presented as a double-page spread with a clear, easy-to-follow diagram supported by succinct explanatory text. The range of titles, by authors who are experts in their field so guaranteeing authoritative and accurate coverage of the contemporary curriculum, covers basic sciences through to clinical specialties. The 2nd edition of *Physiology at a glance*, by Jeremy Ward and Roger Linden, provides a concise introduction and revision text for physiology, applicable to all introductory physiology courses.

For information on the complete *At a glance* series visit: www.blackwellmedstudent.com

The Journal in jeopardy?

In his *Short History of The Physiological Society 1926–1976* WF Bynum includes extracts from the minutes of the Editorial Board of *The Journal of Physiology*. Some indicate the problems encountered by *The Journal* during and after the Second World War. The Report for 1940 says 'No difficulties have so far arisen between the Editorial Board and H.M. Board of Censors; and the Editors regard the acceptance of their guarantee that a paper entitled "The electric organ of the torpedo" contained no matter which might be used by the enemy towards a more effective prosecution of its naval warfare, as a telling symbol of mutual confidence and understanding.' Bynum speculates that 'Perhaps the Censor would have been more concerned had he noticed that one of the authors of this particular paper (W. Feldberg) was born in Hamburg.' In 1948 when paper supplies were still limited EN Wilmer suggested 'that anyone exceeding the current average length of eleven pages per paper was behaving antisocially.'

Bynum W F (1976). A short history of the Physiological Society 1926–1976. *J Physiol* **263**, 23–72.

Ann Silver

Secretarial substitution

Before the advent of word processors most would-be authors were very reliant on secretarial help. Typists did wonders with appalling handwriting but those with no scientific background sometimes produced interesting statements. In one Babraham draft, the author likened lung compliance to the behaviour of a balloon in a string bag; in the typescript, balloon became baboon. A messy comma in one of my own drafts meant the phrase 'but Ho, Paddle & Freeman (1965) reported . .' was rendered rather more dramatically as ' but Ho! Paddle & Freeman (1965) reported . .'.

Some of the developing technology had interesting foibles. The optical character recognition software initially used in the Aberdeen Office of the then *Quarterly Journal of Experimental Physiology* would helpfully suggest alternatives to unfamiliar words. It once enlivened a manuscript by substituting 'erotic' for 'aortic'.

Editorial imagination

The abstracts submitted to the 1993 IUPS Congress in Glasgow – over 3500 of them – raised some alarming images, including the rotation of subjects on a barbecue. A bit of lateral thinking conjured up a human centifuge. A few years ago the same process was applied to 'renal laundry'; this led via 'washing' and 'cleansing' to clearance. Recent light relief includes 'immunocreativity', 'neuromoral' and 'europeptides'.

Ann Silver

Physiology at the Nobels

Although the Physiology or Medicine 2008 Nobel Prize went to medical discoveries, specifically in virology, one holder of a PhD in Physiology was a 2008 Nobel winner. This was, as most readers will know, Roger Tsien of UC San Diego, joint winner of the Chemistry Prize for his work on Green Fluorescent Protein.

http://nobelprize.org/nobel_prizes/chemistry/laureates/2008/press.html

Roger Tsien is well known to physiologists not just for his work with GFP, but also for his development of dyes like Fura-2, among many other seminal contributions to working out optical methods for observing and perturbing cell signalling.

"Graduate students are the pluripotent stem cells of biology. [University] Faculty are...well, basically terminally differentiated... the only options left for them are apoptosis and necrosis." 2008 Nobel Laureate Roger Tsien speaking at UC Berkeley in March 2001. Quote from the Berkeley Science Review.

http://sciencereview.berkeley.edu/articles.php?issue=1&article=backpage

100 years ago in *J Physiol*

A mammalian spinal preparation

C. S. Sherrington (1909). *J Physiol* **38**, 375–383.

The June 1909 issue of *The Journal of Physiology* contains a paper by one of the most revered of all the physiologists of the late 19th and early 20th century, Sir Charles Scott Sherrington OM FRS (1857–1952). Sherrington's status among his own scientific contemporaries is attested by his near one hundred nominations for the Nobel Prize, which he finally won in 1932, together with his friend Edgar Adrian. The nominators, who can be viewed on the Nobel Foundation's website, spanned 30 years (1902–32), and included many other Nobel Laureates. Another indication of Sherrington's scientific stature comes from the tone of his many obituaries. The one in the *Journal of Neurophysiology* begins:

"The Journal records with deepest regret the death... of Sir Charles Scott Sherrington who, almost single-handed, crystallized the special field of Neurophysiology which this journal aims to foster."

All physiology undergraduates, and most medical students, still hear Sherrington's name in the context of spinal reflexes, to the elucidation of which he devoted much of his working life. Sherrington eventually became Waynflete Professor of Physiology in Oxford, where both the physiology building and the street it stands on bear his name. However, his key period of productivity as a scientist was the 18 years he spent in Liverpool between 1895 and 1913, when he published 19 of his 40 *J Physiol* papers. Here is Adrian, writing in 1957 on the centenary of Sherrington's birth:

"It was when [Sherrington] held the chair of Physiology at Liverpool that he was at the height of his powers as an investigator... it was in that period that he gave a new aspect to the study of the nervous system by the precise analysis of its performance" (Adrian, 1957).

Adrian also gives a neat summary of the key early discoveries:

"One [of Sherrington's Liverpool discoveries] was the... proof that at least a third of those [nerve fibres] which enter a muscle are not efferent fibres producing motor effects, but are afferent from sense organs within the muscle, signalling tension and movement to the central nervous system. The other was his demonstration that even in the simplest

reflexes the contraction of muscles promoting the movement involved a simultaneous relaxation of those opposing it."

Adding:

"The term negative feed-back was invented much later but Sherrington had long ago established its importance for the nervous system."

The 1913 paper is, as its title indicates, a description of an isolated spinal cord preparation. Sherrington was in his mid-50s but still a virtuoso experimenter, working alone or with the assistance of a skilled personal technician, George Cox, whom he himself had taught (see e.g. Tansey, 2008). As a student, Sherrington had trained initially for the exams of the College of Surgeons, and had later been both an anatomy demonstrator and a teacher of histology. His skills in dissection technique and knowledge of anatomy were central to his life's work of mapping neural pathways. Sherrington begins the paper:

"A difficulty often felt by those studying spinal functions in [higher] animals... is the want of a preparation which [is] reliable, resistant... and obtained easily, and without great expense of time. After some experience I find the procedure described below yields a preparation fulfilling [this]. The procedure was first devised two years ago for purposes of enquiries into spinal reflexes; experience of its advantages in that work has led to its introduction into general use in the Laboratory. Many purposes other than the study of spinal reactions are well served by it. In consequence of its success here, directors of other Laboratories... have adopted its employment in their laboratories, and find [it] reliable and valuable. Examples of the preparation were demonstrated at the Physiological Society's meeting in this Laboratory in December of last year.

The... whole procedure [of setting up the preparation] occupies about six minutes...

The preparation affords exceptional facilities for investigating reflexes employing the skeletal musculature... The period over which the reflexes can be observed well extends in my experience to ten hours and even longer."

The rest of the paper consists of examples of the reflex activity recorded. As the passage above suggests, Sherrington's spinal cord preparations became a mainstay of teaching reflexes in physiology departments. The methods were described in his highly influential laboratory manual *Mammalian Physiology* (1919) which was still in use into the 1970s (see e.g. Maynard, 2009).

Sherrington, who wrote prolifically, penned a number of articles expounding his views on scientific education. He was a committed believer in learning physiology as a hands-on practical science:

"Paradoxical though it may sound, the more skilfully a demonstration experiment is performed the less from it do some students learn."

(from the Preface to *Mammalian Physiology*). He also argued that the sheer wonder of science was best imparted by those with experience of doing research themselves.

Sherrington's writings, though lucid, can appear a bit wordy to a modern eye, especially on less straightforwardly scientific matters (he produced philosophical writings and even poetry). But Sherrington could add the occasional touch of self-deprecation to his insight. Responding to some visitors to Oxford in the 1920s on what he saw as the challenges for scientific education, he made the following remark, just as apt 80+ years on:

"After some hundreds of years of experience we think that we have learned here in Oxford how to teach what is known. But now with the undeniable upsurge of scientific research, we cannot continue to rely on the mere fact that we have learned how to teach what is known. We must learn to teach the best attitude to what is not yet known."

Austin Elliott

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Sherrington was elected to The Physiological Society at the tenth Annual Meeting in 1885.

UK's leading biology organisations agree to unification

BIOSCIENCES FEDERATION

INSTITUTE OF BIOLOGY

Members of the UK's two leading biology organisations, the Institute of Biology (IoB) and the Biosciences Federation (BSF), have voted overwhelmingly in favour of unification to form a single organisation, the *Society of Biology*. This positive development takes the IoB and BSF a step closer to the creation of an organisation that combines the expertise of the learned societies and other biology organisations with the professional skills of the IoB and its individual members.

The Government's Chief Scientific Adviser, John Beddington, said 'I am delighted to hear this news. The Life Sciences have suffered in the past through fragmentation. The future health and wealth of this nation will depend increasingly on progress made in the biological sciences, and it is excellent that the scientists involved are now all pulling together.'

The move towards creation of the Society of Biology coincides with Lord Drayson's establishment of a team, within the Department for Innovation, Universities and Skills, which will carefully monitor the UK's standing in biotechnology and its applications. Dame Nancy Rothwell, Chair of the Interim Council of the Society of Biology, said 'The vote of the membership demonstrates significant confidence in the work undertaken by many during the past few years to bring about this unification. The Society of Biology will have a sufficient critical mass to enable it to speak with authority over the breadth of topics covered by modern biology, and we look forward to working closely with Lord Drayson's team.'

Martin J Humphries, Chair of the Biochemical Society, said 'I welcome this decision because it will facilitate greater cooperation between the learned societies that represent UK Biology. The resultant synergies from these interactions will improve the ways in which learned societies represent their members, whether they are based in the UK or elsewhere in the world.

A clear majority of IoB members voted in favour of the move at the Institute's 60th Annual General Meeting. Raymond Dwek, who will be the last President of the IoB, said how pleased he was that the members had put the best interests of their science first. 'The Institute's proud and productive 60 year history will make a valuable contribution to the development of the new body in the years ahead.' Member organisations of the Biosciences Federation voted without objection at their Annual General Meeting.

The forthcoming integration of the Institute of Biology and the Biosciences Federation offers a unique opportunity to create the leading organisation for biology in the UK. For more information, see: www.newbio.info

Contacts

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Society of Biology

The forthcoming integration of the Institute of Biology and the Biosciences Federation offers a unique opportunity to create the leading organisation for biology in the UK. Our mission is to create a single unified voice for UK biology, representing the discipline and its practitioners. We will champion discoveries in biology and support their translation to health, economic, social and environmental benefit, promote understanding, learning and communication in biology, develop partnerships within the UK and overseas, and provide the widest possible support to our membership. Our goals are to build upon and develop the strengths of both IoB and BSF, and seize new opportunities to broaden our range of influence and scale of activities.

The Institute of Biology (IoB) is an independent and charitable body charged by Royal Charter to represent UK biologists and biology. It has around 12 000 individual members and over 50 specialist learned societies 'affiliated' to it. The Institute's Mission is to promote biology and the biological sciences, to foster the public understanding of the life sciences generally, to serve the needs of its members, to enhance the status of the biology profession, and to represent its members and the biology profession as a whole to government and other bodies in the UK and abroad.

The Biosciences Federation (BSF) is a single authority representing the UK's biological expertise, providing independent opinion to inform public policy and promoting the advancement of the biosciences. The BSF is actively working to influence policy and strategy in biology-based research – including funding and the interface with other disciplines – and in school and university teaching. The BSF is also concerned about the translation of research into benefits for society, and about the impact of legislation and regulations on the ability of those working in teaching and research to deliver effectively. Member societies, of which there are 45 plus 9 Associate Members, cover the full range of biosciences from physiology and neuroscience, biochemistry and microbiology, to ecology, taxonomy and environmental science.

Society update – from the Chief Executive

In past years The Society has planned its activities on a year-by-year basis as our income (which comes primarily from our publishing activities) could not be predicted very far ahead. The movement towards open access publishing for scientific manuscripts was (and still is) regarded as a major potential threat to our income. If libraries and individuals stop subscribing to our Journals, because they are made available for free at the time of publication, the resulting loss of income could ultimately threaten our existence as a Society in its current form!

I am pleased to say that this particular threat has been ameliorated (for a number of years into the future) by The Society signing a publishing agreement with Wiley-Blackwell that guarantees it a healthy publishing income, irrespective of Journal sales. So as long as the credit crunch doesn't push Wiley-Blackwell out of business, The Society can plan ahead, based on a platform of financial security.

Recently, the Executive Committee of Council held its first brain-storming meeting to consider its long-term vision for the future of The Society. These discussions will be continued and developed with the full Council during the year.

Some key features that emerged from these preliminary discussions were:

Modernisation of The Society

We need to continue to be forward looking and developing our science to reinforce the position of physiology as **the** integrative bioscience (from molecule to whole body). But we must also maintain the excellence traditionally associated with The Society, so that it is seen as the leading light in the discipline. Continuing the modernisation of communication of society information and of scientific advances to our members and to the outside world is essential and we need to build our technical and public relations expertise to do this.

Increasing our ambition in all areas of current activity

This includes education, external affairs, meetings and publications, as well as international activity and new areas, such as translation of basic research through to clinical advances. We should continually be looking for ways to increase the scope and range of our activities, while maintaining our focus on the pivotal importance of physiology. A range of specific proposals were made by the Chairs of all The Society Committees as to how they could increase their activities and gain maximum value from them.

Increasing our sphere of influence

To meet the challenges facing us, it was felt to be essential that we engage with a broader range of people: clinical colleagues, teachers, pharmaceutical companies, and the relevant research councils as well as continuing to broaden our appeal to younger scientists (undergraduates, postgraduates and post-docs) studying physiology. Furthermore, we should continue to develop our links with other like-minded societies, and to increase our political and international influence.

Communication

It was agreed that The Society needs to ensure that communication with colleagues is clear and transparent. This has become harder as traditional physiology departments have disappeared, but also becomes more important if the disappearance of departments is not to result in the disappearance of the discipline. Without excellent communication it will be difficult to engage properly with physiologists, and thus to ensure the future of the discipline. Many routes were discussed to achieve this – email, web surveys and the website; communication via departmental Society representatives, SIG convenors and HoDs groups; the magazine and newsletter (see box) and building on the opportunities afforded by attendance and advertising at our meetings.

One further topic of discussion in the Executive Committee has been whether we should seek to share accommodation with other learned societies. The Biochemical Society, the Society for Experimental Biology and The British Ecological Society have been seeking a building for joint purchase and occupation. These three societies have recently made an offer for a building that could accommodate a number of other societies and The Physiological Society was approached to see if we wished to participate. This proposal was discussed extensively but, in addition to some practical difficulties, the Executive Committee thought that our strategy should be to share with societies with more commonality of membership and scientific interests. This does not, of course, rule out the possibility of The Society co-habitating with other groups consistent with our long-term strategy for expanding our sphere of influence as discussed above.

Mike Collis

For Society Noticeboard, see p. 64.

E-newsletter for Members

You will have noticed that we have recently introduced an e-newsletter for our Members. This started out as a monthly communication and we are considering a move to fortnightly editions based on feedback on its value. The newsletter is a brief screen shot reminder of deadlines that are approaching and points readers to the relevant section of the website for detailed information. We hope that by using this regular 'alerting' service we can reduce the number of emails sent to Members as we all suffer from email overload these days. We welcome any feedback on the newsletter and its frequency and general feedback on the way The Society communicates with its membership. Please email comments to mcollis@physoc.org

Membership activities

2009 has already been a busy year, with The Society's membership activities geared up to recruiting new members, particularly in the Undergraduate Associate category. Originally launched in 2007, the student membership category was introduced in recognition of the need to encourage budding physiologists, welcome them to the community and facilitate their career. We hope our activities will raise awareness of The Society and enhance our already diverse membership of over 2600 Members.

The Membership Services team has been actively recruiting through visits to universities around the UK and Ireland, providing an information point to potential members as well as career support to our student members. The purpose of our visits to undergraduates is to talk about The Society, benefits of membership, resources we offer students and how to get together to develop a student society under the umbrella of The Physiological Society. If requested by students and society representatives, an additional careers session in the form of a CV workshop is also organised. Although most universities have careers services providing this support, the workshops are considered to be a valuable service and are always positively received – raising self-awareness and providing the knowledge and skill to write an effective CV.

Trinity College Dublin.

University of Leeds.

The promotional visits are also a great opportunity to find out a little bit more about what current and potential Members of The Society are interested in, in terms of Member benefits. Taking feedback on board, travel grant funding for students has been launched this year, enabling students to apply for up to £100 a year for support to attend meetings and conferences. We will continue to develop resources and benefits for all our membership categories.

Universities we visited in early 2009 included King's College London, University of Leeds, Trinity College Dublin and the University of Westminster. The Physiological Society, through individual undergraduate societies, can help support the career development of physiologists and we are very much looking forward to hearing from Members who would like to arrange for us to visit their institution this year.

If you would like to arrange a visit or discuss the opportunities of establishing an undergraduate society, please feel free to contact me on:

+44 020 7269 5726 or email at imagre@physoc.org

For more information on Society activities please visit: www.physoc.org

Irrum Magre

International capacity building in science and technology. The potential role of learned societies

In the last few years, the global development agenda has moved forward to embrace the importance of science, technology and innovation in helping to address the crucial development issues facing the world today, including climate change, health, infrastructure development, the building of sustainable livelihoods and the elimination of poverty. Science and scientists are now seen to be integral to this global effort, and it is recognised that a key aim has to be to develop local scientific capacity in developing countries to enable them to address pressing local issues and build sustainable economies. Local solutions are needed for local problems. This can only be achieved by supporting effective grassroots initiatives, tying these closely to real local needs, and embedding them in supportive governmental science policy and funding frameworks.

Learned societies of every discipline are in a unique position to contribute to this agenda. Such societies are quite different from the many other ways in which science is organised, whether through government funding agencies, universities or science-based industries. In essence they are 'clubs of scientists', whose raison d'être is to capacity build their respective disciplines, and in some cases they have been doing this very successfully for centuries. As clubs, they are often not overly hierarchical, and are naturally organised as extended networks of scientists with strong links at grass-roots level. Many of the older ones, founded centuries or decades ago to serve their immediate scientific communities, have naturally extended towards having an international membership, and have been quietly supporting budding scientists in the developing world before the main international aid agencies saw the importance of this. Such programmes have not been developed by sometimes remote policy makers, but have the advantage of having been

Apparatus arriving at a physics teacher training workshop in Rwanda funded by the Institute of Physics.

driven by the expressed needs of their memberships.

Learned societies have the potential to help in capacity building at many levels. As well as being able to directly respond to local scientists needs and develop initiatives at grass-roots level, they also often have relevant experience of advising on science policy at governmental level. Learned societies and their members know how to set up and run scientific journals (many of which are still closely connected to the societies that created them), work with the publishing industry, run events on topical research issues, provide networking and career development support, train students, work with schools and universities to encourage young people to study and take up careers in science, and engage with the media and the general public on crucial issues of public concern. The Royal Society conducted a survey of some current capacity building initiatives in learned

Francis Gatete, training another teacher to use the optics apparatus in Rwandan School.

societies in 2007. This indicated that because of lack of funding, many of their international capacity building programmes, though successful, have remained small. Their potential is far from being realised!

Since 2007, The Physiological Society has reviewed this topic. A concept paper is now available which looks at the evolving international development agenda supporting capacity building in science and technology in developing countries. It reviews some current developments in major players such as the World Bank and the Department for International Development, and outlines how learned societies might be able to effectively contribute to the development of long-term, sustainable, grass-roots, research and teaching communities in their disciplines in developing countries that are closely networked with their international colleagues. Our research indicates that this could help tackle many of the capacity building problems being encountered by international development agencies, by providing long-term, stable professional networks underpinning their research programme and other initiatives.

The Physiological Society is developing an example of a programme of support, initially focused on Africa, which might be developed for physiology, a fundamental discipline that underpins medicine and bioscience. Support for this, and its related biomedical disciplines, is vital in helping developing country scientists tackle local health issues. However, we believe that the programme principles being developed are equally applicable to learned societies across the entire spectrum of the natural, engineering and social sciences, addressing other vital issues to developing countries such as environment, climate change, agriculture, energy, civil society etc. We are currently working with a Biosciences Federation (BSF) Working Group on Capacity Building to co-ordinate parallel new initiatives from its member societies. The Physiological Society and the BSF are also working with societies outside the biosciences area, including the Institute of Physics (IOP) and the Royal Astronomical Society (RAS), to develop new models and explore the issue with policy makers and funders. We will be holding a joint meeting for learned societies at the RAS in the summer to brainstorm how we might take this agenda forwards.

If you would like a copy of our concept paper, more information on the forthcoming meeting at the RAS, or to discuss this further, please contact me at ebell@physoc.org

Liz Bell
(this article was first published in *CaSE Newsletter*)

The joint meeting of the learned societies on capacity building will take place at the Royal Astronomical Society in London on 2nd June, and a report on it will appear in a later issue of Physiology News.

The new invisible college: how globalisation is changing the landscape for scientific collaboration

The Royal Society Science Policy Centre Policy Lab, 3 March 2009

The Royal Society has recently re-organised its science policy activities and seems to be doing lots of new and exciting stuff. As part of this they have been organising a new monthly series of science policy labs. This was the first one I had attended, and I was thrilled to discover how closely it complemented our independent thoughts on how learned societies should get more involved in capacity building for international development.

The key note speaker was Caroline Wagner from George Washington University's Center for International Science and Technology Policy. She talked about her recently published book '*The New Invisible College*' which Calestous Juma has described as a 'forceful assault on the traditional edifice of science policy'. Her basic thesis was that we need to recognise how science has developed over the centuries if we are to tackle science policy issues effectively. Science has got so complicated that it is returning to its 17th century roots of invisible colleges i.e. informal networks of scientists. This is now the biggest force at global level and a network systems model is needed for its governance. In the 17th to 19th centuries, learned societies and other professional associations drove scientific development on a networking model. Then in the 20th century the principal driver became scientific nationalism, with governments

funding and organising 'Big Science' to an unprecedented degree. However, ICTs have now created distributed networks of people working together in a dynamic way. It is these large, informal networks that are now really driving science, and governments have very little influence on the social interactions involved. These self-organising, grassroots networks need support and encouragement, particularly in developing countries where the model used in international development has tended to be to try to replicate the formal structures of 'Big Science' without sufficient attention to the needs of the supporting networks. Scientists in developing countries need help to get linked into the real scientific system of networks.

The discussion gave me a wonderful opportunity to flag how we were already thinking about this, and that we and other learned societies, were very well placed to provide the necessary support to such networks. Our club of scientists model worked very well in the early stages of developing science in the West, and is now poised, if we can get appropriate funding, to repeat the feat in helping developing countries grow their SET capacities. I was also given another opportunity to follow this up in a subsequent Royal Society event on the 25 March where the Nobel Laureate Harold Varmus, advisor to President Obama, was talking about 'restoring science to its rightful place'. In talking about how supporting science in every respect was a priority in addressing the global credit crunch, climate change issues etc, he didn't mention support for scientific capacity building in international development. So I asked him whether this would be a priority under the new regime, bearing in mind its vital importance in helping developing countries address their own and global needs. He agreed that it should be.

So these two meetings left me feeling optimistic that the science policy agenda may now be moving in our direction, and that over the next few years we may be able to leverage some funding to support networks of scientists in developing countries. However, it is early days yet.

To help take this forward, I am looking to make contact both with Members based in the UK with experience of working in Africa, and Members based in Africa. I look forward to hearing from you at: ebell@physoc.org

Liz Bell

The Otto Hutter Physiology Teaching Prize

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

We are proud that Otto Hutter has agreed to lend his name to The Society's new prize. Otto began his career in the 1940s as a scientific technician at the Burroughs & Wellcome labs in Kent, before completing a BSc and PhD at UCL. As well as having a successful research career, Otto has helped spread physiology education to a wider world, both internationally and through teaching innovation. At Glasgow, he pioneered perhaps the first, fully integrated electrophysiological lab for junior teaching. He is also a virtuoso of small group teaching, famous for throwing the blackboard chalk as an inducement to do some of the board-work yourself!

The new prize will be officially launched at Physiology 2009 in Dublin, with a nomination deadline of 30 September 2009; the recipient of the prize will be notified by the end of 2009 and will receive £1000 in prize money (£500 of which should be used for teaching resources) .

We hope this prize, and Otto Hutter's example as an enthusiastic physiology teacher, will encourage continued development and excellence in teaching. For more information about the Otto Hutter Physiology Teaching Prize, please visit our website at www.physoc.org/teachingprize or contact education@physoc.org.

Exciting pupils about biology

When academics, researchers and undergraduate students work together on schools outreach programmes, there is potential for everyone to benefit. Fiona Wyllie, Innovation and Engagement Officer at Cardiff University School of Biosciences, explains some of the initiatives she has introduced to encourage scientists at every stage of their career to excite primary and secondary school pupils about biology and the possibility of studying the biosciences further, and to help bridge the gap between school and university.

Exciting experiences in the lab are high on the list of things young people enjoy about science and are frequently cited as the aspect that switches them on to further study. So, much of our secondary schools' engagement work centres on inviting groups to 1-day workshops which not only illustrate the work of research groups at Cardiff University, but are also very practically orientated. One such workshop, '*Using killer genes to fight cancer*', represents a research interest of Richard Clarkson, RCUK Fellow in the School of Biosciences. Pupils learn about this project by participating in activities analogous to those undertaken on a daily basis by scientists in Dr Clarkson's group. The pupils separate and subsequently visualise DNA fragments by gel electrophoresis, then genetically transform bacterial cells to give colonies which fluoresce green. They examine sections of tissue under the microscope to discover how genes can be investigated as potential therapeutic agents. Both postgraduate and undergraduate students are heavily involved in providing advice and assistance during the practical sessions and we have found that this creates a good informal atmosphere which encourages visiting pupils to

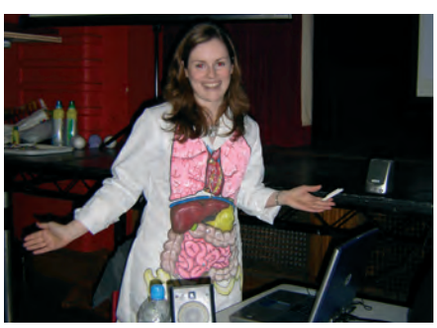
chat to the students about courses and university life. This workshop has also addressed the problem that practical work, although 'hands-on', is too often 'minds-off'. We are currently running an alternative form of this workshop as part of a Royal Society Partnership Grant (http://royalsociety.org), which involves pupils having to design and then implement their own experimental plan. We have run one of these workshops so far and found that, with some help, pupils designed good insightful plans and were extremely eager and motivated to engage in their very own experiments.

These workshops have several aims: to improve achievement at the end of AS year exams, to encourage subsequent retention in A level biology and to encourage further study. Another initiative aimed even more directly at addressing the problem of poor exam achievement has been the creation of the first annual 'South East Wales Biology Challenge' this year. I got together with three local biology teachers and a scientist from a local bioscience company, GE Healthcare, to compile an inter-schools AS revision quiz representing 'real-life' research and commercial applications, interspersed with rounds based on TV shows. A team of undergraduate students bravely formed an 'eggheads' team, which all of the competing schools delighted in subsequently beating on the evening of the quiz! One of my rounds illustrated well a typical biomedical research group and interests – the varied composition of the team, the reasons for doing the research, many cutting edge techniques, subsequent conclusions and benefits for society. The other round emphasised the connection of our research with the everyday world – how understanding more about how protease enzymes work can help to enhance the taste and texture of cheese, lead to better and more environmentally friendly washing detergents and potentially get away from burning fossil fuels. The teachers ensured that the questions were very curricularly orientated and that their pupils were motivated to begin early revision in the hope that they could bring glory to their particular school and take home the coveted challenge trophy, bought with a £1000 Special Merit Award from the Rolls-Royce Science Prize. This money also funded

a fancy buzzer system, which ensured fair play and entertaining sound effects throughout the quiz!

Two years ago we created a new and compulsory 'Biology in Society' module for all Final Year undergraduates in the School of Biosciences. As well as introducing students to the nature and importance of public engagement across all sectors of bioscience employment, the module also deals with issues associated with a range of controversial bioscientific topics. Optional coursework introduced this year gave interested students the opportunity to not only learn more about one such topic, that of stem cell research, but to also run their own ethical discussion session with GCSE classes in local schools. Training for this session provided students with materials aimed to inform and stimulate discussion amongst the pupils and ideas on how to facilitate the session and effectively work as a team. Specific sessions were then set up, available students organised into teams of four or five and a car hired for the trip, which did not involve any accompanying University staff. The sessions helped to improve students' communication, teamwork and time-management skills and also provided teachers, who have seen this topic only very recently introduced into the curriculum, with relevant ideas.

It is well recognised that children go through their primary school years with a generally high interest and enthusiasm for science, but it is often a time when this positive approach is not sufficiently built upon, especially if the knowledge and confidence of the teachers involved are inadequate. For some years now, we have attempted to capture the innate scientific fascination of 10/11 year olds by inviting five or six local schools (around 240 pupils over 2 days) to the University for a day of engaging workshops and small 'lectures'. This year we had over 12 workshops on offer, ranging from several with live organisms (toads, frogs, springtails, earthworms and various pond invertebrates) through to one showing why snot becomes green and another which involves scraping off pupils' own cheek cells and viewing them under the microscope. Undergraduate students were also involved in running their own workshops, either going with ideas and materials provided for them or, in one case, designing and implementing their own ideas on the brain. Smoking awareness was highlighted through an interactive play performed by myself and undergraduate students, which uses brightly coloured organ tunics to illustrate the health dangers of cigarettes and a theme of athletic performance to show other problems with being persuaded to smoke.



We hope to build on the experiences and successes of the last year and increase the overall number and the variety of practically-orientated workshops on offer to schools. I find that when our researchers learn that I can provide audiences, venues, advice and/or ideas on how to engage pupils with their research and substantial assistance with applying for outside funds, that they often become very keen on getting involved. In addition, we hope to involve undergraduate students in as great a number of activities as possible, not only to provide role models to the visiting pupils but also to emphasise the importance of engaging with outside audiences and to give them some of the skills required to do this well.

Fiona Wyllie
Innovation and Engagement Officer, Cardiff University

The Discovery Zone at Leeds – an explosion of science

Picture a sports hall filled with 24 science stations, manned by over 70 research staff (PhD students right up to Professors) from the University of Leeds; a sea of colour and unusual objects, awash with enthusiastic chatter and anticipation. Crayfish in tanks are limbering up for races. Academics are pumping up airbeds to balance children on. Twelve foot models of neurones, made from ropes, balls and funnels are being tested. Plants are everywhere, forming small jungle areas interspersed with bats, insects and... spectrophotometers! The doors open and 120 school children arrive, looking around in eager expectation at all the impending activities. The children are efficiently assigned to their stations, the staff await the onslaught, the noise levels increase and the fun begins! This is the Discovery Zone at the University of Leeds!

This 2 day event, kindly sponsored in part by The Physiological Society's new outreach scheme, enabled nearly 500 school children aged 8–14 to experience science phenomena first hand. Using models, live animals, machines, fact sheets and brain power, the pupils encountered the evolution of ant colonies, LEGO proteins, the wonders of saliva, real brains, skeletons, maths problems, insect defence systems and the importance of a healthy heart. They extracted DNA from fruit and thought about its role in humans, then made DNA bracelets. They experienced different kinds of energy and its uses. Each station provided some simple take-home messages, learnt through hands-on experiences. It is amazing how staff members managed to make intra- and intermolecular bonding relevant and understandable by making goo – the message being re-enforced beautifully by practical fun. There is nothing like the opportunity to blow things up to interest children whilst others really enjoyed learning about the exquisite sensitivity of the tips of our fingers, enabling us to read Braille and identify objects, just based on touch. In the year of a celebration of evolution, pupils learned about adaptations of plants to enable survival by changing ways of seed dispersion.

The extremely positive feedback from university staff, accompanying teachers and most importantly the pupils, illustrates the importance of running such events at university and the rich and varied rewards. Through funding from The Physiological Society and BBSRC, transport was provided to the event, making it accessible to all schools, regardless of socioeconomic status. Many children were therefore experiencing a university setting and staff for the first time. One child described the event as a 'wonderland' whilst another school reported that pupils had gone back to school buzzing so that others who had not attended organised a delegation to the headteacher to demand to be taken!

This comment from an eminent professor who helped to run a station summed up the feelings of all the staff when he reported 'This was a really great occasion, it was gratifying how many children said they really enjoyed the experiments – isolating DNA was 'cool' – and several said they wanted to be scientists when they grew up!'

Overall, a success for schools, the University and most importantly, science, thanks to The Physiological Society.

Sue Deuchars
Academic co-ordinator and pipe-cleaner neurone constructor extraordinaire
Institute of Membrane and Systems Biology, University of Leeds, Leeds

The outreach grant scheme is open to all Members and Affiliates of The Society who would like to communicate the excitement of physiology to young scientists and the wider community. For more information, please visit our website or email education@physoc.org

New international grant schemes

The Society has launched three new grant schemes to support research and teaching in international physiology. **International Junior Research Grant** – intended to support junior researchers overseas (outstanding physiologists at senior postgraduate or post-doctoral level) and replaces the Junior Fellowship scheme. **International Senior Research Grant** – intended to support senior researchers overseas, and replaces the Centres of Excellence scheme. The **David Jordan International Teaching Fellowship** – aimed at teachers/learning support staff to give them an opportunity to visit an institution of their choice in order to develop or acquire teaching methods of benefit to the teaching of physiology. For more information of the three new schemes please visit www.physoc.org.

Hot topics meeting in pharmacology and physiology 2009

The 'hot topics' addressed at The Joint Meeting of the British Pharmacological Society and The Physiological Society, 26–27 March 2009 at the University of Warwick included some feedback from the recent Research Assessment Exercise (RAE), managing the research and teaching divide and how to improve National Student Survey (NSS) scores. The presenters were Jeremy Pearson (KCL), Ian Kitchen (Surrey), Graeme Henderson (Bristol), Clive Orchard (Bristol), Mike Spyer (UCL), Paul Hubbard (HEFCE) and Ian McFadzean (KCL).

The RAE requires a great deal of effort from all concerned, yet its output tends to result in very little shift in money actually distributed to universities. Submissions showed that translational research from the lab bench into clinical practice is rarely evident in a single research centre – it takes several centres working in collaboration. Four year PhD programmes were valuable, and longer-term funding (programme grant level or above) tended to correlate well with output quality. Some panels did check the ISI citations for papers submitted, and found it to be a useful guide to paper quality.

The RAE will be succeeded by the Research Excellence Framework (REF). It is hoped that the new system will involve less work for Higher Education Institutes (HEIs) and will involve bibliometric analysis and other indicators. Hopefully it will be an improvement on the RAE system of examining self-selected outputs which can over-value the average research quality of an HEI. HEFCE are trying to move towards assessing institutions rather than individuals. Elements of peer review will be kept to support the other analyses, with assessments from special groups feeding into a smaller number of expert panels. The economic and social benefits of research will be increasingly important.

The RAE has also had impacts beyond funding on HEIs. A classic example has been on the research/teaching divide in departments, where HEIs have tended to link kudos to success in research rather than teaching. Ideally research should inform teaching and encourage the next generation, but too often the 'stars' have zero or very low teaching commitments. Ideally all staff should be able to contribute to all areas of a department's work, with better use being made of support staff, delegating to them to make their work more interesting. Post grads and post docs should also be used more to help their CVs and broaden their education. Innovation in teaching should be encouraged, and professional rewards should perhaps be made contingent on teaching as well as research. It should always be remembered that universities are not research institutes even if they are research led – financial viability actually comes from teaching.

National Student Survey scores are also more of an issue for departments in the context of the general quality assurance framework for higher education. Students are increasingly using them to help choose an HEI. Attention to issues affecting an institution's score were highlighted, for example, an increase in security in HEIs can make it very difficult for students to access staff and visit research labs; reductions in small group sessions notably in practical work; and increasing assessment burdens on staff resulting in too little individual feedback. Feedback can be improved in a cost-effective manner by such strategies as using student peer assessment, debriefing surgeries on exam papers etc. An issue highlighted in the discussion was that departments are dealing with increasingly unrealistic student expectations; students need the differences between universities and sixth form colleges explained to them early on.

Liz Bell

Do we need more multiskilled scientists and engineers to manage economic recovery and change?

At the Parliamentary and Scientific Committee Meeting on 12 March 2009, Lord Drayson, the Minister of State for Science and Innovation, said that the answer to this question was a resounding yes. He described his own background as an engineer and a businessman, propelled into this arena through the support of a joint ESRC/SERC funded PhD studentship in the 1980s. The social science elements of his engineering degree training helped him to put his work into a broader context, and set him up for his subsequent success in commercialising science. In his view, SET is vital for rebalancing the economy post the Credit Crunch. Investment needs to be maintained in both pure and applied research. We need to develop a society literate in SET, and HEIs will need to produce graduates capable of working well with people from other disciplines to drive innovation. It could be a great opportunity to get the excellent SET graduates previously lost to the City back into universities! The question about increased flexibility in degree provision sparked off a lot of debate on resourcing implications.

This meeting rather focused on the potential contributions from the physical and engineering sciences, but the Technology Strategy Board did highlight the need for new treatments to tackle chronic diseases in an increasingly ageing population. This gave me the opportunity to highlight the importance of the biomedical sciences in many different areas relating to the economy, and to ask them to keep developments in e.g. Systems Biology in mind.

Liz Bell

The Journal of Physiology

The Journal of Physiology Editor-in-Chief Elect appointed

The Physiological Society is delighted to announce that Michael Rennie (Professor of Clinical Physiology at the University of Nottingham) has been appointed as Editor-in-Chief Elect for *The Journal of Physiology*.

Mike Rennie is internationally known for his work in human metabolism, especially protein metabolism and the mechanisms of growth and adaptation to physical activity/inactivity, disease and ageing. He has a long history of publishing high impact papers in *The Journal of Physiology*. Mike has a deep interest and involvement in all aspects of physiology and has served on *The Journal's* Editorial Board (1996–2003) and on the MRC Physiological Medicine and Infections Board Grants Committee. He also has an illustrious history of service to The Physiological Society, having been a Trustee and a member of a number of Society committees including, as chair, the Committee of Heads of Department of Physiology for the UK. He was the Professor Sir George Lindor Brown Prize Lecturer of The Physiological Society in 2004.

Mike will take over as Editor-in-Chief of *The Journal* when William Large finishes his tenure in the post on 30 June 2010.

Annual Review Prize Lecture

The 2009 Annual Review Prize Lecture has been awarded to a *Journal of Physiology* Editor, Stephen G Waxman of Yale University. Steve's lecture is entitled *Fire, fantoms and fugu: sodium channels from squid to clinic*, and will be published in *The Journal* later in the year. Since receiving the award from The Society, Steve has also been awarded the US Department of Veterans Affair's William S Middleton Award for Outstanding Achievement in Biomedical Research, the VA's highest scientific honour.

Both awards recognize Steve's significant research achievements in physiology and pathology relating to spinal cord injury, multiple sclerosis and painful nerve injuries. Steve trained as both a neurologist and a neuroscientist and his research builds upon the 'molecular revolution', to develop new therapeutic strategies that will restore functions such as sensation and the ability to walk after spinal cord, nerve and brain injury. His research was the first to show the changes in molecules within nerve cells that permit remissions – recovery of previously lost functions such as vision and motor control – in multiple sclerosis, and he has identified key molecules that are responsible for pain after nerve injury and spinal cord injury.

In his role as Editor of *The Journal of Physiology*, Steve has contributed to the launch of Clinical Perspectives, *The Journal*'s initiative to link the basic science reported in its research papers to clinical treatments. *The Journal of Physiology* congratulates Steve on his awards.

The Annual Review Prize Lecture will be delivered on Thursday 9 July, 1800–1900, at Physiology 2009 in Dublin.

Experimental Physiology
Translation and Integration

Early Career Author's Prize

Are you eligible to compete for the *Experimental Physiology* Early Career Author's Prize 2009?

The *Experimental Physiology* Early Career Author's Prize is being introduced to reward early career authors who publish outstanding research papers in *Experimental Physiology which best meet the journal's remit of translation and integration. See* http://ep.physoc.org/misc/ifora.shtml#policy

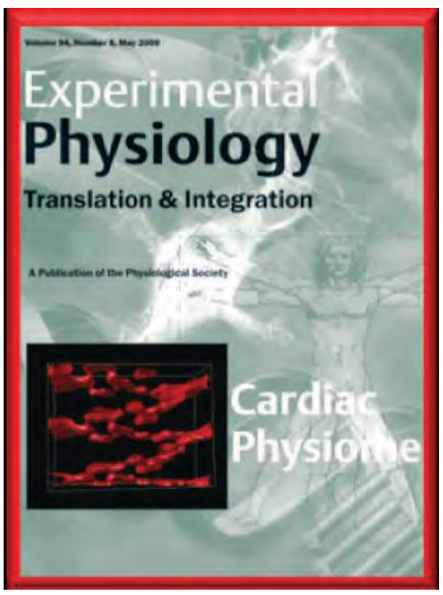
The first prize, sponsored jointly by The Physiological Society and the publishers, Wiley-Blackwell, will be $1000, There will be a runner's up prize of $500 .

Entries will be judged by the journal's Editorial Board and the results will be published in *Experimental Physiology* and *Physiology News* early in 2010. The winners will be invited to a formal presentation at *Physiology 2010* The Society's main meeting in Manchester 28 June –2 July.

Entries are invited from scientists who are either the first or last author of a research article published in *Experimental Physiology* in 2009. Authors will be asked if they are eligible to enter when their paper is accepted for publication. We hope to offer a similar prize to early career authors of papers published in 2010. Applicants must have received their research degree (MD, PhD or equivalent) less than 6 years before submitting the paper. In the case of candidates who have both a MD and PhD the date of the most recently awarded degree should be used.

Cardiac Physiome Themed Issue

The May 2009 issue (94:5) of *Experimental Physiology* is a Cardiac Physiome themed issue organised by Nic Smith, Peter Hunter and David Paterson.



In addition to providing a snapshot of current cardiac physiome work, the articles converge on three themes that are central to the translation and integration focus of *Experimental Physiology*, specifically: the application of modelling tools across spatial scales; facilitating the re-use and application of mathematical models in experimental contexts; and the translation of modelling work for understanding human physiology and pathophysiological function.

See: http://ep.physoc.org/content/94/5.toc

Exchange of Views

Is it really only our kidneys that control blood pressure?

The April 2009 issue of *Experimental Physiology* hosts a lively debate between two groups of world-leading experts. In the first ever published dialogue on the topic, Drs Montani and Vliet, and Drs Osborn, Averina and Fink share their opinions with us and criticise each others theories. Their frank exchange of views provides an interesting and informative summary of the latest research into how blood pressure is controlled.

The problem of high blood pressure has reached pandemic proportions, causing premature death through heart attacks, strokes and kidney disease in a third of the UK population. For decades, scientists have battled at length over its cause yet still cannot agree; is the kidney or the brain to blame?

When blood pressure increases, the kidneys respond by extracting extra water and salts into the urine, causing blood volume –and hence pressure – to fall. But special nerve pathways mean the brain can also regulate urine production and hence influence blood pressure. So which organ is really in charge? Montani and Vliet argue that controlling blood volume is the key, as the kidney automatically makes more urine as blood pressure increases. However, Osborn and colleagues remind us that the cardiovascular system is controlled by multiple mechanisms including the automatic part of the nervous system, which directly controls the kidney. They also update us on a plethora of new findings supporting a role of the nervous system in controlling blood pressure long term. Both groups acknowledge that new mathematical models are needed that incorporate both the kidney and the brain control systems. So the question of whether it is the kidney or the brain that has a firmer grip on the reins for controlling blood pressure may have to wait for a mathematician to answer.

Read this Exchange of Views free online: http://ep.physoc.org/content/94/4.toc

The Journal of Physiology Symposia 2009

Novel insights into oestrogen actions

Wednesday 8 July 2009

At The Physiological Society Annual Meeting, Dublin, Republic of Ireland.

Dynamic aspects of functioning membrane proteins

Friday 31 July 2009 (10:00–12:30)

At IUPS, Kyoto, Japan.

Physiological regulation linked with physical activity and health

Friday 31 July 2009 (10:00–16:30)

At IUPS, Kyoto, Japan.

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 these, and other symposia visit http://jp.physoc.org

Prize Lectures 2009

The following Prize Lectures will be delivered in 2009:

Annual Public Lecture	Stephen O'Rahilly	Physiology 2009, Dublin, Wednesday 8 July, 18.15–19.15
Annual Review	Stephen Waxman	Physiology 2009, Dublin, Thursday 7 July, 18.00–19.00
Bayliss–Starling	Gero Miesenboeck	Physiology 2009, Dublin, Wednesday 8 July, 12.15–13.00
Biller	Gavin Stewart	Newcastle Themed Meeting, September
GL Brown	Mark Boyett	Various (see the website for schedule)
Hodgkin–Huxley–Katz	Eric Kandel	Physiology 2009, Dublin, Thursday 9 July, 12.15–13.00
Michael de Burgh Daly	Colin Nurse	Physiology 2009, Dublin, Friday 10 July, 12.15–13.00
Paton	Diethelm Richter	Physiology 2009, Dublin,Tuesday 7 July, 17.30–18.30

New journal websites

The Journal of Physiology and *Experimental Physiology* are hosted through HighWire, a non-profit division of Stanford University Libraries. We are pleased to announce that our journal sites have now been upgraded to HighWire's new *Web 2.0* platform.

Whereas Web 1.0 sites merely published content for a visitor to view, Web 2.0 aims to facilitate communication, participation and collaboration between sites, between users and sites, and between users themselves. The new platform infrastructure is designed to cooperate with emerging web services and technologies and also to anticipate future website developments.

Some of our new features include:

Abstract preview – mouse-over the table of contents and search results page for an instant pop-up preview of the article abstract, without leaving the page.

Figure expansion in place – figure and table thumbnails can be enlarged from within the article.

Tag-along navigation – the navigation box follows alongside as you scroll down the article page.

Feature hideaway – author affiliations, related links and other article enhancements can be expanded or hidden. Article enhancement preferences are remembered when the user next visits the site.

Popular-articles list – a list of the Most Viewed and Most Cited articles is readily available.

Related-articles search – from within an article, users can click to search for articles by author, keyword, or subject classification.

Easier scanning and reading – better positioning of the title and abstract, improved text fonts and formatting, plus quick previous/next links to scan by article section make it fast to scan an article online.

Look and feel – completely revamped design, incorporating Society branding together with new, more intuitive, site navigation.

The Journal of Physiology new homepage.

Experimental Physiology new homepage.

The new user interface is a flexible three-column design that places many features at your service without taking attention away from the substantive page content. Features most closely associated with the page content are placed closest to it. A major goal of the new design is to keep you in context as you conduct your research.

New Table of Contents design.

Looking to the future, the upgrade ensures our content will work with a wide variety of Web 2.0 applications, feeds, widgets, and web services and expanded branding. It also gives end users the possibility of features such as social networking, forums, and a number of content delivery options through mobile platforms. The upgrade makes our content more accessible, and more portable than ever, allowing us to move information to where the user is and will enable our readers to take the latest scientific research with them.

We hope you enjoy the new features this platform brings, and invite you to send us your comments and feedback at:

http://jp.physoc.org/feedback

The Journal of Physiology
(http://jp.physoc.org)
Experimental Physiology
(http://ep.physoc.org)

Liam McKay
IT & Communications Manager

New staff member in the Publications Office

Laura Buck, a recent MPhil graduate in Biological Anthropology from the University of Cambridge, will be working with Ann Watson in the Distribution Office within the Publications Office in Cambridge, taking manuscripts through the review process.

Laura replaces Ed Sexton, who has taken on much of the work of Linda Rimmer.

Hans Meves

1925–2008

Hans Meves was born on 13 September 1925 in Berlin. After school and military service on the eastern front from 1943 to 1945, he read medicine at the University of Marburg. He received his doctor's degree in 1951 and started his scientific career with Hans Lullies whom he followed to the recently founded Saar University in Homburg and later to Kiel. During these years with Lullies, who himself had made impedance measurements in nerve before the war, he published seven full-length papers mainly on the effect of carbon dioxide and hydrogen on nerve and muscle fibres.

In 1957 he went to Stockholm for 6 months to work with B Frankenhäuser who had been a close co-worker of Alan Hodgkin. There he investigated the effect of Mg^{2+} ions on isolated single nerve fibres and also had long discussions with Frankenhäuser about the dramatic advances in membrane physiology initiated by the ionic theory.

After Meves returned to Kiel, he continued to work with myelinated nerve fibres and started an analysis of after-potentials, for which the ionic theory provided testable predictions. In the autumn of 1959, he spent 2 months with R Stämpfli, who by then was the Professor of Physiology in Homburg. Together they perfected the technique of dissecting single nerve fibres. This collaboration was the start of a close friendship that lasted until Stämpfli's death in 2002. In 1961, Meves joined Stämpfli's lab in Homburg where he remained until 1967.

Stämpfli had established valuable international connections that were sorely missed in Germany after the war. Among the many foreign visitors to Homburg was Richard Keynes who recommended Hans Meves to Alan Hodgkin. A short visit to Cambridge followed and he became one of the few foreign co-workers of Alan Hodgkin at the Marine Biological Laboratory in Plymouth. Exciting experiments were done late into the night. Collaborating with 'the great man' (Peter Baker's name for him) was certainly the most important experience in his scientific life. During the Plymouth season in 1962, Hodgkin, Baker and Meves explored the effects of low ionic strength on action potentials. They used

Hans Meves, Kiel 1968.

the perfused axon technique, a method whose results had added strong support to the ionic theory and paved the way for Hodgkin's Nobel Prize in Physiology or Medicine in 1963.

In the 1963 season, Hodgkin and Meves were joined by Knox Chandler for further studies of low ionic strength and of ionic selectivity of the sodium channel using the voltage-clamp method. Meves and Chandler had one more season in Plymouth in 1965 (see Knox Chandler's piece). For these studies, Stämpfli generously gave Meves leave for Plymouth and helped to obtain financial support. The time at Plymouth was always followed by 1 or 2 months in Cambridge, where the data were evaluated and manuscripts written. The Meveses enjoyed their stays there, in the ancient city with its college traditions, where they were received with remarkable hospitality by the Hodgkins and Keyneses. Occasionally I myself joined the Meveses for dinner at the French restaurant in Hills Road and on visits to London.

In 1967, Meves was appointed full Professor of Physiology in Kiel. Three years later, however, he left his Chair in protest against the turbulence at the German universities which severely disrupted scientific life. Although he had two attractive offers in the States, he eagerly accepted the invitation to join the staff of the Marine Biological Association, first as Principal and later as Senior Principal Scientific Officer. He spent 10 happy and scientifically fruitful years there, exempt from administrative and teaching obligations.

Hans Meves' research was concerned with the selectivity (structure) and the activation/inactivation mechanisms (gating) of ion channels, along the lines developed in Hodgkin and Huxley's famous four 1952 publications. Many experiments were carried out on voltage-clamped perfused squid giant axons where the properties of Na currents could be compared with the asymmetrical displacement currents that are thought to arise from the voltage sensors of Na^+ channels; the effect of venoms of a scorpion were also studied on Na^+ currents. In other experiments, Ca^{2+} currents and the effect of 4-aminopyridine on K^+ currents were investigated. This work, partly done with younger colleagues, appeared mainly in *The Journal of Physiology*. During this period, he and his wife enjoyed entertaining at their house. They fed many of the young, and usually very hungry, people who came to Plymouth, among them Peter McNaughton and Roger Tsien.

In 1980, Meves returned to Germany as the successor of R Stämpfli in the Chair of Physiology at Homburg and became active in a Sonderforschungsbereich on membranes. He continued studies on the sodium channel using the frog node of Ranvier instead of the squid giant axon. He remained the classical electrophysiologist, however, working alone or with only one co-worker at his 'stand'.

In 1990, he retired but continued to do experiments, now with an analysis of the effects of lipid mediators such as prostaglandins on neuroblastoma x glioma hybrid cells. For this work, which was published in a number of papers in various journals, he learned the patch clamp technique. His successors, first A Konnerth and then J Rettig, kindly provided space and help in various ways. For some time he also enjoyed financial help from the DFG.

Twice in the early 90s he collaborated with RD Keynes at the Station Biologique in Roscoff (France) which he enjoyed greatly. Throughout his scientific career, he was always an enthusiastic experimenter.

Hans Meves became a Member of The Physiological Society in 1965 and was a member of the Editorial Board of *The Journal of Physiology* from 1975 to 1984.

Hans Meves's interest went beyond science. He was an avid reader of literature – both classic and modern – and he loved the arts and the theatre. He was a great walker and each year would spend time among the lakes and mountains of the Engadine in Sils Maria.

Towards the end of his life, during the illness which he bore with great courage and fortitude, when he could no longer go to the lab, Meves continued working at home. His last paper *The arachidonic acid and ion channels* was an update of his pioneering review from 1994; it

appeared online on 16 June 2008 in the *British Journal of Pharmacology*. Hans Meves died on 25 September 2008. For 53 years he was married to Dorothea Altmeyer.

Hans-Christoph Lüttgau

Ruhr-University, Bochum

Knox Chandler adds:

Hans Meves and I first worked together at the Laboratory of the Marine Biological Association in Plymouth during the 1963 squid season, when we set out to study the selectivity of the Na channel and effects of low internal ionic strength in voltage-clamped internally perfused squid giant axons. The experimental schedule started with the 3–4 pm arrival of iced mantles from freshly caught squid. After the nerve bundles containing the giant axons had been removed, we would go to the common room for afternoon tea with other squid workers, if any, and various staff members of the laboratory. Experiments would begin after tea and go on until all (or almost all) the nerves had been used, sometimes past midnight. By the time the last experiment was finished and the film developed (photographs of voltage and current records on an oscilloscope), the local restaurants would be closed and Hans would take me to his flat where Dorothy would prepare supper for us at whatever time we arrived. I was always grateful to Dorothy for her delicious impromptu meals.

The next day we would examine the films from the previous day, do rough analysis, and discuss what to do next. It was clear that Hans loved doing experiments. He was always full of energy, in good spirits, and ready, even at 2 am, to start a new experiment and carry it out with care and precision. He brought a lot of intelligence to the research and was a good teacher. I came to like and respect him enormously.

Since squid came only on Monday to Friday, Saturdays were more relaxed. After analysis and various chores, Hans and I would meet Dorothy to have a good dinner in town, usually at the Octagon, sometimes joined by Richard Keynes or other visiting squid workers. The conversations were always lively, especially after a couple of glasses of beer or wine, when Hans could be persuaded to tell one of his entertaining stories. During one such dinner Dorothy, I think, wondered aloud why Alan had not won a Nobel Prize. We talked about possible reasons but never imagined that the Prize would be announced the following week.

Hans Meves and Knox Chandler, Plymouth 1964 (photo by Peter Baker).

Hans and I had a second squid season in 1965 when we studied Na currents in perfused axons without K in the internal and external solutions. After that, we never had the opportunity to collaborate again. Hans visited us once in New Haven, in the late 1960s as I recall. Several times after that, after Hans had been made Professor in Homburg, my wife Caroline and I visited Hans and Dorothy in Homburg, once with two of our teenage daughters. Hans and Dorothy always showed us great hospitality in Homburg and we have fond memories of the wonderful times we had together.

The Society notes with regret the death of Pierre Dejours and Phillip Poole-Wilson. A full appreciation of Phillip Poole-Wilson will hopefully appear in the next issue.

Noticeboard

Non-Society meetings

Bone Research Society/British Society for Matrix Biology Joint Meeting
University College London, UK
14–16 June 2009, www.bsmb.ac.uk/brs/

SEB Annual Main Meeting 2009
SECC, Glasgow, UK. 28 June–1 July 2009, www.sebiology.org

3rd International Symposium on Physiology and pharmacology of temperature regulation
Matsue, Japan. 23–26 July 2009
http://www.med.shimane-u.ac.jp

BPS Summer Meeting
University of Edinburgh, UK
8–10 July 2009, www.bps.ac.uk

Congress of the European Association for Clinical Pharmacology and Therapeutics
Edinburgh, UK, 12–15 July 2009
www.eacpt2009.org

IUPS 2009
Kyoto, Japan, 27 July–1 August 2009
www.iups2009.com

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

Society Noticeboard

Upcoming deadlines for Scientific Meetings – 2009

For a comprehensive overview visit the website

Festschrift Symposium in honour of John A Russell
University of Edinburgh (1 July)

Physiology 2009 – University College Dublin, RoI (7–10 July)
For updates visit http://www.physiology2009.org/

Muscle physiology: function and dysfunction
Young Physiologists' Symposia, Dublin (7 July)

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)
Abstract submission and registration opens on 22 June

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

http://www.physoc.org/grants
New international grant schemes:
http://www.physoc.org/international

Themed Meeting of The Physiological Society

Epithelia & Membrane Transport

Including a focused symposium on *Epithelial form, function and environment*

6-8 September 2009
Newcastle University, UK

Abstract submission & Registration opens 22 September 2009

Development of epithelial structures
Nick Wright (London, UK)
David Tosh (Bath, UK)
Diane Barber (San Francisco, USA)
Markus Affolter (Basel, Switzerland)
John Sayer (Newcastle, UK)

Physiology and pathophysiology of epithelial solute transport
Yuichi Sugiyama (Tokyo, Japan)
Stephan Broer (Canberra, Australia)
Peter Agre (North Carolina, USA)
Edith Brot-Laroche (Paris, France)
Dianne Ford (Newcastle, UK)

Epithelia under stress
Richard Boucher (North Carolina, USA)
Ole Petersen (Liverpool, UK)
Marshall Montrose (Cincinnati, USA)
James M Anderson (North Carolina, USA)
Tomas Ganz (Los Angeles, USA)

Biller Prize Lecture:
Gavin Stewart
(University College Dublin, RoI)

Abstract submission closes
27 July 2009

Travel Grant deadline
31 July 2009

Early-bird registration closes & YPBS deadline
10 August 2009

www.physoc.org/newcastle2009

'*Don't look now, Mabel, but the Professor is back from the solvents cupboard*'. Microscope-based histology sessions prove riveting for students and staff (from the School of Medicine Anatomy Museum).

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www.physoc.org