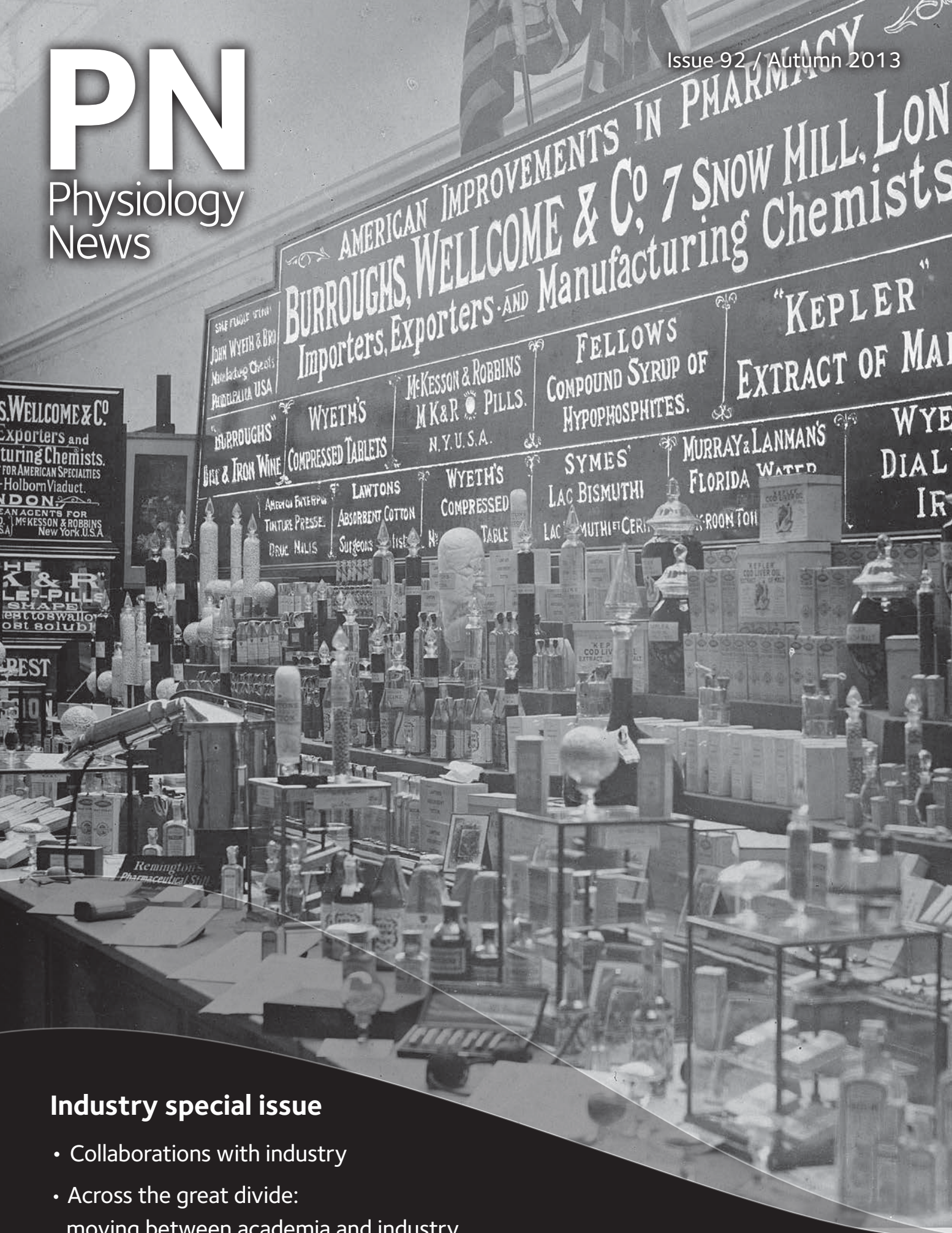
PN Physiology News

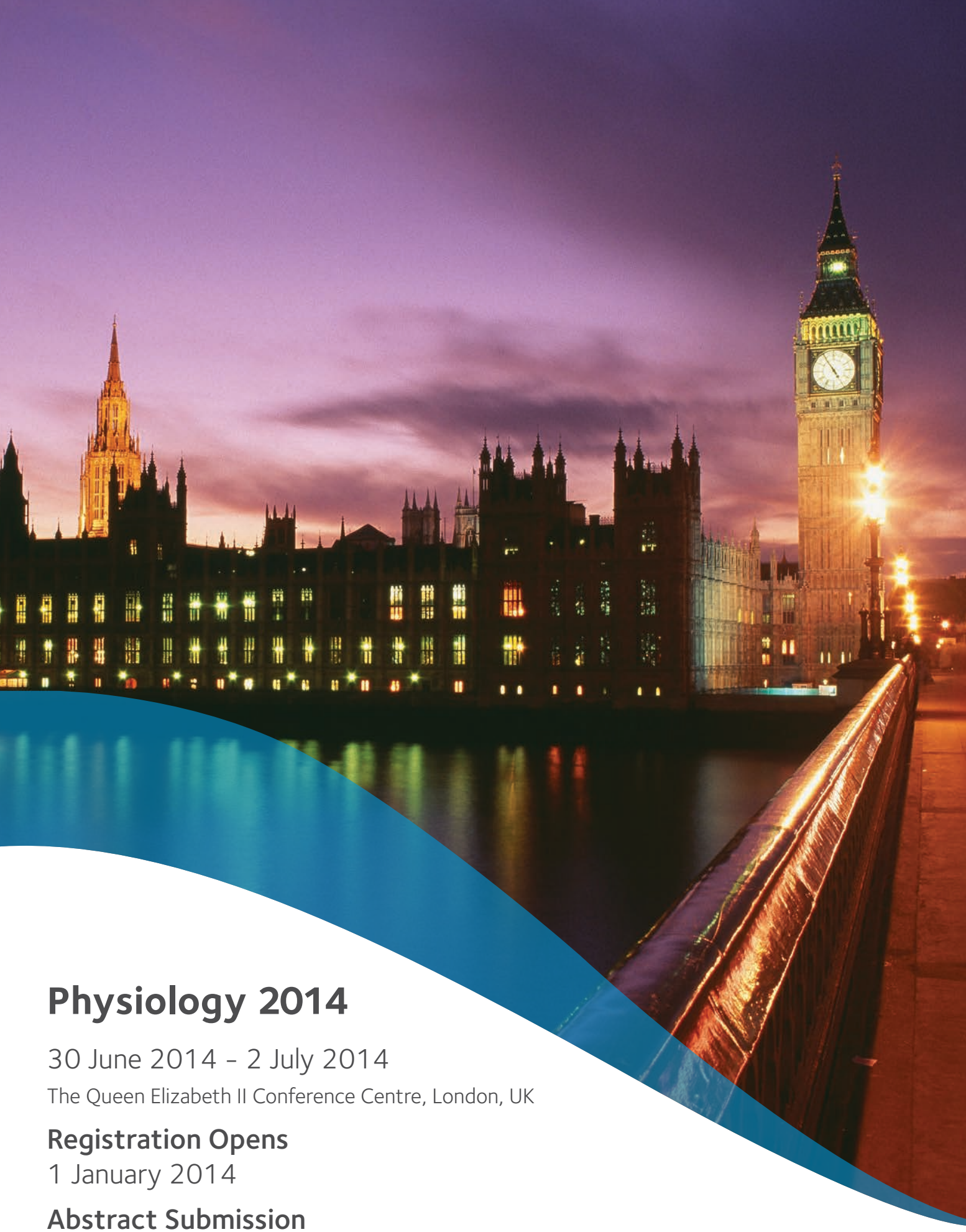
Issue 92 / Autumn 2013



Industry special issue

- Collaborations with industry
- Across the great divide: moving between academia and industry
- How the pharmaceutical industry is changing

The Physiological Society



Physiology 2014

30 June 2014 - 2 July 2014

The Queen Elizabeth II Conference Centre, London, UK

Registration Opens

1 January 2014

Abstract Submission

1 March - 31 March 2014

www.physoc.org/p14

The Physiological Society

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Cover image: Display of products by Burroughs Wellcome & Co.

Credit: Wellcome library, London

Epithelia and Smooth Muscle Interactions in Health and Disease

A Physiological Society joint Themed Meeting in Epithelia & Membrane Transport and Vascular & Smooth Muscle Physiology

Convention Centre Dublin, Ireland
11–13 December 2013

- Airway remodelling
- Gastrointestinal secretion & motility
- Epithelia & smooth muscle ion channels

Plenary speakers

Kim Barrett
(University of California San Diego, USA)

Kenton Sanders
(University of Nevada, USA)

Registration opens 12 August 2013

Abstract submission opens 23 September 2013

Abstract submission closes 23 October 2013

Early bird registration closes 11 November 2013

www.physoc.org/emvs13

Physiology News

We welcome feedback on our membership magazine, or letters and suggestions for articles for publication, including book reviews, from Physiological Society Members. Please email **magazine@physoc.org**

Physiology News is one of the benefits of membership of The Physiological Society, along with reduced registration rates for our high-profile events, free online access to The Physiological Society's leading journals, *The Journal of Physiology* and *Experimental Physiology*, and travel grants to attend scientific meetings. Membership of The Physiological Society offers you access to the largest network of physiologists in Europe.

Join now to support your career in physiology:
Visit **www.physoc.org/membership** or call **0207 269 5728.**

Membership Fees for 2013	**FEES**	
Membership category	Direct Debit	Non-Direct Debit
Ordinary Member	£73	£93
Ordinary Retired Member	-	-
Affiliate	£16	£21
Associate	£36	£47
Undergraduate Join alone (single payment)	-	£15
Undergraduate Join as part of undergraduate society (single payment)	-	£10

Physiology News / Autumn 2013 / Issue 92

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Editorial

Siobhan Dennis

Guest Editor

Welcome to the *Physiology News* Industry themed issue! We hope this issue will be of interest and helpful to a range of scientists, from those finishing their undergraduate degree to senior researchers. There is a wealth of opportunity for academics to collaborate and for partnerships with large pharmaceuticals and small enterprises to be created. Maybe this issue will even inspire exploration of an alternative career or even for you to start up your own biotech!

Pharmaceuticals and biotechs play a large role in the UK economy and the UK currently has the fourth largest pharmaceutical sector in the world (Government strategy plans 2012). About a seventh of the top 100 medicines in use today originated from research in this country – a record second only to that of the United States. As well as providing new medicines for many diseases, the pharmaceutical industry makes a substantial contribution to the British economy, providing income, employment and major investment. The pharmaceutical sector has, over the past decade, consistently generated a large trade surplus for the UK. Not only does this sector make a significant contribution to 'UK PLC' it is also responsible for employing thousands of people in the UK – mostly in highly skilled research and development roles. The industry also has numerous collaborations with university researchers and supported nearly 1000 pre- and post-doctoral students in 2011.

Despite the major achievements of the pharmaceutical and biotech industry in the UK, its future is less clear and probably less rosy. Life sciences industries have declined within the UK recently. This is a significant concern and in the long term results in the UK losing out on the benefits of future discoveries and on many employment opportunities. The loss of Pfizer from its Sandwich site, announced in 2011, was a sign of the difficult decisions faced by even the largest of the pharmaceutical companies in the face of patent expiry on some of their most successful drugs. There are also UK specific factors that have contributed to this decline, such as the length and cost of clinical trials in the UK and changes to the drug pricing system. Key to future investments in the UK by multinational pharmaceutical and biotech companies will be the availability of young biological scientists with excellent academic training in the skills needed to discover and develop new medicines. The health of the pharmaceutical industry in the UK is intimately linked to the quality of the training and education young life scientists receive in this country.

The way the pharmaceutical industry operates is changing. Companies can no longer rely on 'blockbuster' drugs such as Eli Lilly's Zyprexia and Pfizer's Lipitor. As the patents on these expire, companies face a cliff edge of falling income. In the face of these challenges the industry is evolving to new business models. There is more collaboration between companies such as the Innovative Medicines Initiative, which is a joint venture between the European Union and several companies of various sizes. Collaborations with academics are becoming more important and proving to be beneficial to all involved, resulting in rapid advancements. As large companies downsize their in-house research capabilities they are increasing their outsourcing activities, which provides a real opportunity for academic groups to forge new collaborations. The drive by industry to work much more closely with leading academic groups is illustrated by the relocation of some of Pfizer's and AstraZeneca's research activities to Cambridge and the establishment of a Research Park at the Glaxo site in Stevenage.

The need for new drugs has never been greater with an ageing population, epidemics of obesity and diabetes, stressful lifestyles and the emergence of resistant pathogens. We need to keep the UK attractive to pharmaceutical companies for research activities and we can support this by ensuring a steady supply of excellently trained graduate and postgraduate scientists and an academic sector that conducts world-class research and welcomes industrial collaborations.

Industry has incredible and unique working environments to offer and hopefully this issue will allow you to explore how pharmaceutical companies function, and perhaps what opportunities there are for you in the life sciences industry.

Rod Dimaline delivers his last report as Honorary Treasurer

Elections to Council

The following have been elected by Members to serve on The Society's governing Council for four years with effect from the Annual General Meeting (AGM) on Wednesday 24 July 2013.

- Sue Deuchars
- Lucy Donaldson
- Anne King
- Prem Kumar
- Mike Ludwig
- Rachel Tribe

It was an extremely competitive field this year and we hope that unsuccessful candidates will not be discouraged from standing in the future. The successful candidates' proposers and supporting statements can be found online at **www.physoc.org/council-election-results-2013**

In addition, the following individuals have been elected by Affiliate Members to attend Council and committee meetings, representing Affiliates.

- Fiona Hatch
- Ruth Norman

Out-going members

The following individuals ended their term on The Society's governing Council at this year's AGM. We thank them for their service.

- Rod Dimaline
- Stephen Bolsover
- Julian Dow
- Stuart Eggington
- Andy Trafford
- Michael White

Honorary Members

The following individuals have been elected as Honorary Members of The Society. You can read more about the work that earned them this recognition on pages 44 & 45.

- Sir Martin Evans
- Richard Boyd
- Frances Ashcroft
- Mordecai Blaustein
- Philippe Ascher
- R Alan North

Annual General Meeting 2013

The 2013 Annual General Meeting (AGM) was held at the Symphony Ballroom, Hyatt Regency Hotel, Birmingham on Wednesday 24 July 2013. The meeting was chaired by David Eisner, who is BHF Professor of Cardiac Physiology at The University of Manchester.

The meeting saw Anne King, Program Director for Human Physiology at The University of Leeds, succeed Rod Dimaline as The Society's Honorary Treasurer.

Jonathan Ashmore, The Society's President, reported that 2012 was a landmark year for The Society, with the negotiation of a new contract with Wiley-Blackwell through to the end of 2018, and the purchase of, fit-out and move to The Society's new home at Hodgkin Huxley House (HHH) all completed within the year.

Giving his final report as Honorary Treasurer, Rod Dimaline explained the financial thinking behind the historic purchase and move to HHH by The Society, which made sound financial sense, in terms of both reducing annual costs and providing a long-term investment. He also told Members that the spend on charitable activity had increased by 21% and publishing income, which remained strong, was now guaranteed to the end of 2018 through the new contract with Wiley.

For the first time in The Society's history, the Chief Executive was invited to present a report to the meeting. Philip Wright noted that it was a great privilege to be asked to do so. His report focused on three areas of activity for the coming year: the Health of Physiology project; development of a membership strategy; and a review of governance.

The Editors-in-Chief (EiCs) of *The Journal of Physiology* and *Experimental Physiology* – David Paterson and Paul McLoughlin, respectively – presented reports to the meeting. Members expressed concern about both falling Impact Factors and The Society's use of this contentious metric to promote the journals. It was noted that the EiCs and The Society had recently signed up to the San Francisco Declaration on Research Assessment (DORA), which describes deficiencies in how we evaluate research output and proposes alternative approaches.

Sue Wray was unable to attend as Editor-in-Chief of *Physiological Reports*, so a report was presented on her behalf by Philip Wright. He noted that this new journal is a milestone, being both Open Access (OA) and the first that The Society has launched (having inherited *The Journal of Physiology* and *Experimental Physiology*).

Members vote at the AGM

Further detail on the AGM can be found at **www.physoc.org/agm2013-report**

Members also asked questions pertaining to:

- Summer placements and the funding that The Society makes available for these
- The Research Excellence Framework and how The Society might seek to mitigate any negative impacts on the field of physiology
- The falling number of demonstrations at Society events since 2005

Further detail on Member questions can be found at **www.physoc.org/agm2013-questions**

Physiology meets the public at IUPS

With the arrival in Birmingham of over 3000 physiologists from across the globe for the 2013 IUPS Congress, we had a fantastic opportunity to connect local members of the public with physiology and the world-leading researchers attending the conference.

Alongside the scientific programme, we held a number of free hands-on physiology activities for the public outside the conference centre, within the Mobile Teaching Unit (MTU) and a marquee, from 22 to 24 July.

The MTU is a lorry managed by the AIMS CETL within the University of Bristol and part-sponsored by The Society. It houses a range of clinical equipment that take physiological measurements, and regularly hosts activities for schools and science festivals, where it's proven a great hit over the years.

In collaboration with Hannah King, the MTU's Outreach Assistant Teacher, we organised a range of activities suitable for all ages, including:

- a lung function test with a vitalograph to examine the relationship between height and vital capacity
- a grip strength test to examine how grip changes with age
- a homeostasis activity to look at whether core body temperature changes during exercise
- a number of anatomical models to explore internal organs and their function

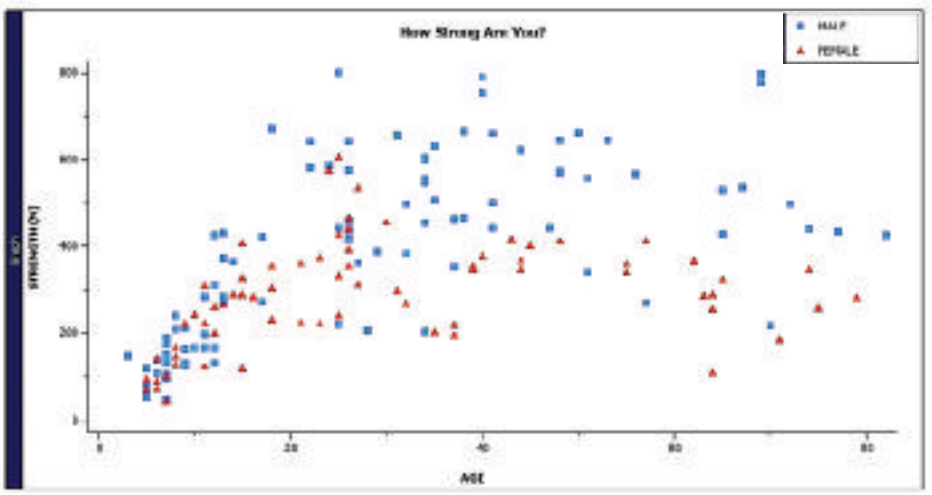
The grip strength test was kindly provided by ADInstruments and run by Kevin Evans, one of their Application Scientists with a background in exercise physiology. We were also joined by *The Bionic Ear Show*, an interactive model of the ear developed by *Science Made Simple* and Deafness Research UK, and presented by Tobin May.

Equipped with an army of enthusiastic volunteers comprising over 40 delegates, including several plenary and keynote speakers, we set out to bring physiology to the public, and not even some stormy weather could deter us. We received a steady stream of visitors of all ages throughout the three days, as shown by figures collected in the grip strength test alone (figure below).

Amongst the visitors were two hugely competitive five-year-old twins, who were disappointed to discover they had almost equal grip strength; a 77-year-old who had half of his right lung removed 70 years ago and, although he had reduced respiratory function, could still do everything and had excellent grip strength for his age; and a 22-year-old who said he'd failed science at school but then, after taking part in these activities, said, "science is quite cool actually!" One visitor even claimed the activities were "better than the Sea Life Centre", a popular local attraction for families.

We were, of course, delighted to receive such wonderful feedback and the volunteers also enjoyed their experience, with some expressing a desire to do more activities in future. Lauren Salo, from the University of Bristol, volunteered on Wednesday and says, "Getting to explain physiology to people by 'doing' things reminded me why physiology is so much fun – a totally energising experience!"

We'd like to offer our sincerest thanks to everyone who contributed to making this event such a success and, in particular, the volunteers for their generosity and enthusiasm.



Physiology Feed

Bringing you snippets of the latest intriguing research

New Tree of Life?

The Pandoravirus contains 2500 genes and at 1 µm in size is now the largest known virus, raising questions about a possible 'Fourth Domain' of life. Dwarfing most viruses, which are 50-100 nm with ~10 genes, only 7% of its genes have database matches, hence the tribute to Pandora's Box in the name.
DOI: 10.1126/science.1239181

Teeth from urine

Chinese scientists have grown 'teeth' from stem cells found in human urine. The 'tooth-like structures' created contained dental pulp, dentine, enamel space and enamel organ, but were not as hard as natural teeth.
DOI:10.1186/2045-9769-2-6

Workouts rewire fat cells

The epigenetic pattern of genes that affect fat storage in the body changes with regular exercise, this study of 23 overweight and previously inactive men shows.
DOI: 10.1371/journal.pgen.1003572

Endless cloning

Improving upon the somatic cell nuclear transfer (SCNT) technique that created Dolly the sheep, Japanese researchers have shown cloning mice from a single drop of blood is possible. Current SCNT technology even has the ability to clone up to 581 healthy mice from a single donor over 25 consecutive generations.
DOI: 10.1095/biolreprod.113.110098 and DOI: 10.1016/j.stem.2013.01.005

Blood test for Alzheimer's

Researchers have found a way to diagnose Alzheimer's disease via a simple blood test that is over 93% accurate. The study looked at microRNAs in the blood of 48 Alzheimer's patients and 22 control participants. They found 12 microRNAs in the blood which were present in markedly different levels in people with Alzheimer's.
DOI:10.1186/gb-2013-14-7-r78

continued on next page

Picking offspring's sex

Recent evidence suggests that mammals can select the gender of their offspring. Environmental cues (e.g. hierarchical status) can shift gender ratios in order to increase the next generation's chances of reproductive success. For the mother, males represent a high-risk strategy but may have many offspring, while females are the safest bet for guaranteeing some offspring.
DOI: 10.1371/journal.pone.0067867

Stem cell reprogramming without genetic manipulation

Researchers have successfully reprogrammed adult tissue to become cells as versatile as embryonic stem cells using chemical compounds only, excluding the need for additional genes that could increase the risk of dangerous mutations.
DOI: 10.1126/science.1239278

Real-life 'Inception'

False memory implantation has been achieved in mice utilising optogenetic techniques. Researchers were able to induce memory recall of a familiar safe environment when in an alien setting while simultaneously applying mild foot shocks. Upon return to the familiar environment behavioural signs of fear were observed, where in fact it was never shocked in reality.
DOI: 10.1126/science.1239073

Mind control

Harvard researchers have developed a non-invasive brain-to-brain interface to control the movement of a rat's tail. First the human's brain activity is read by an EEG-based brain-to-computer interface. The signal is then transmitted into the rat's brain by a focused ultrasound-based computer-to-brain interface which stimulates neurons. The process has also recently been replicated in humans to move another persons' hand. Here transcranial magnetic stimulation was used (http://homes.cs.washington.edu/~rao/brain2brain/).
DOI: 10.1371/journal.pone.0060410

If you spot some interesting research that you'd like to share with your fellow Members, please send it to us at **magazine@physoc.org**

Winning a Rob Clarke Abstract Award

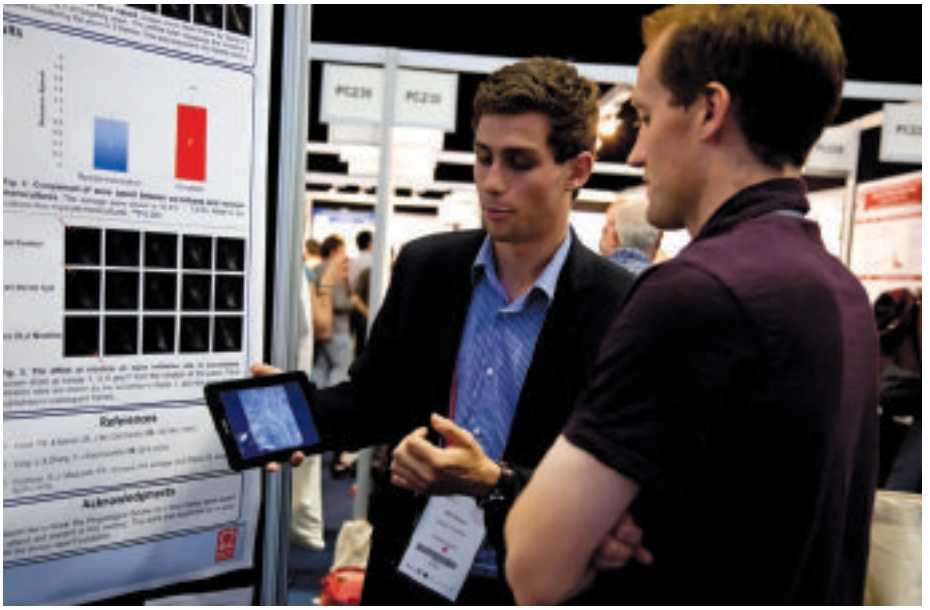
Amy Sharkey
University of Oxford, UK

As part of my intercalated medical degree, I recently completed a research project looking at the effect of neuronal stimulation on cardiomyocytes in neuronal-cardiomyocyte co-cultures. My lab encouraged me to apply for a Rob Clarke Abstract Award, in order to present my work as an undergraduate at IUPS 2013, and I was lucky enough to receive funding to attend the conference too.

At the conference I discovered Rob Clarke Abstract Awards had been granted to around 20 students from all over the world, providing a fascinating insight into how not only medicine but biomedical sciences and physiology are taught in different parts of the world. We presented our posters over two hours, to a panel of judges and also to several other eminent physiologists present at the conference.

Although the presentation initially seemed a daunting process, it was a joy to discuss my work with others interested in the same areas of research, and it was a great way of ascertaining new opinions as to future directions for my research.

The Rob Clarke Abstract Award also covered the cost of attending the congress dinner, which was a great night of food, drink and dancing, and also offered fantastic networking opportunities, as it was attended by scientists from across the globe. I would like to thank The Physiological Society for the opportunity to attend the conference, as well as my lab in Oxford DPAG and my tutors at St. Hugh's College, Oxford, for supporting me.



Policy Corner

Osborne announces science funding settlement

In June George Osborne presented Spending Round 2013 to Parliament, in which he announced that the 'resource' funding for science would be maintained at £4.6 billion for 2015-16. The chancellor also announced that capital funding, which was slashed in 2010, would receive a welcome boost and funding levels would be increased in real terms from £0.6 billion in 2012/13 to £1.1 billion in 2015/16, after which the capital budget is to grow in line with inflation until 2020-21.

The Society broadly welcomed the Government's recognition of the value of science to the UK; however we remained concerned what impact the continuing 'flat cash' resource budget settlement will have on the UK science base and will continue to call on the Government to look to increase funding for UK science. There will need to be another concerted effort by the community around the time of the next general election in May 2015 to ensure that science receives the funding it requires to flourish.

Animal research statistics released

In July the Home Office released the animal research statistics; the headline figures showed an increase of 8% in the overall numbers of procedures used to 4.1 million procedures. This increase was attributed to a 22% increase in the breeding of GM animals. In the field of physiology the numbers of procedures fell by 29% to 430,909 procedures, which is roughly in line with the statistics from 2008-2010. The policy team continue to work with our collaborators both to enhance the regulatory environment and to boost public perception of animal research.

As mentioned in the last edition of *Physiology News*, The Society is represented on the Concordat on Openness in Animal Research, which aims to increase openness and transparency in animal research. The project is now in full swing and it is hoped that the concordat will be released for public consultation by September/October and launched by the end of the year.

STEM disability transition conference

The Society was involved in arranging a highly successful conference highlighting some of the challenges faced by disabled STEM students during the transition phases from 'school to university', 'through university' and from 'university into work'. The conference was held at the Institute of Physics and had a full house with over 70 delegates, comprising representatives from higher education institutes, civil service, learned societies and disability organisations. The organising committee will shortly be publishing a report on the conference, which should provide recommendations on how the transition process for disabled STEM students can be improved.

Women in Science

Three highly successful women in science seminars were held at IUPS and Caroline Wood has provided an in depth review on the sessions on page 12. At these sessions The Society launched a 'Women in Physiology' booklet; thanks must go to Sue Wray who came up with the idea and was very much the driving force for the project. The booklet highlights the career paths of a number of female physiologists and can downloaded from www.physoc.org/diversity.

New Council members join the Policy Committee

Lucy Donaldson

Fiona Hatch

We are delighted to announce that new Council members Lucy Donaldson and Fiona Hatch have joined the Policy Committee.

If you are interested in these or any other policy related issues please contact us via **policy@physoc.org**

Membership Survey 2013

In March and April, we asked Members to share their opinions on our activities through a Membership Survey. The 2013 survey was composed with a view to garnering results that are directly comparable to that undertaken in 2011, and with a view to repeating the exercise every couple of years. This will generate a record of The Society's perceived performance and information that is actionable.

Responses to the 2011 survey have informed our strategic plans and results have been discussed by relevant committees to support decision-making. The 2013 survey will similarly lead our activities over the coming years.

We present here some of the key points to come out of the 2013 Membership Survey, especially related to *PN*. The full results will be available online later in the year.

About you

The total number of responses stood at 561 when the survey closed on 30th April. This represents a very healthy 17.5% of the total membership.

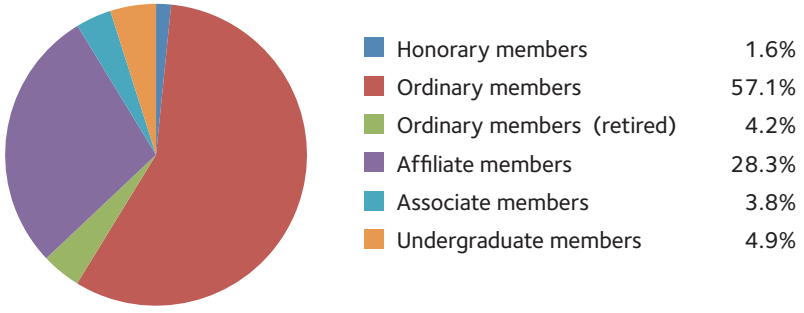
57% of respondents were Ordinary Members, and 28% Affiliates. This compares well with the actual makeup of the membership, at 57% and 31% respectively.

94.7% of respondents said that they were active in research – 47% of whom were also engaged in teaching.

70% of respondents were based in the UK.

Your main policy concern is funding for research.

Membership categories of survey respondents



The Society online

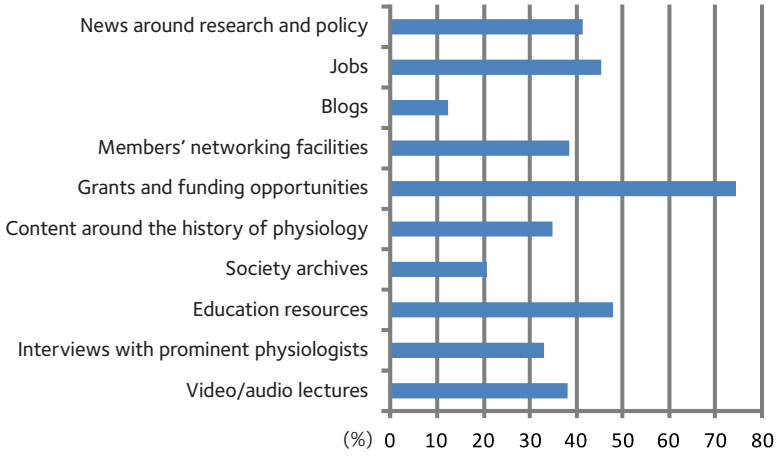
87.2% of respondents rated www.physoc.org 'good' or 'very good' for content, and 73% gave the same rating for the site's user-friendliness.

74.2% wanted to see more grants and funding opportunities flagged up online.

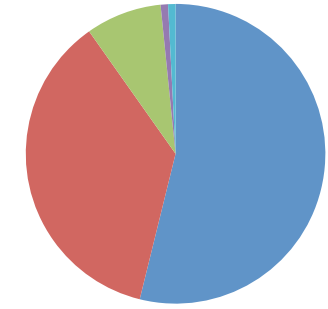
48% of you want more educational resources available through our website.

93.4% of you receive the monthly email newsletter and 75.8% rate is as 'quite useful' or 'very useful'.

What would you like to see more of on www.physoc.org?



How important is Impact Factor in choosing a journal for publication?



Very important	53.9%
Quite important	36.4%
Neutral	8.2%
Not very important	0.8%
Not important at all	0.8%

The Society's journals

We asked you about your publishing activity in order to focus the strategies guiding our three journals; *The Journal of Physiology*, *Experimental Physiology* and *Physiological Reports*.

Over 90% of respondents thought that the reputation of a journal was 'quite important' or 'very important' when choosing where to submit. Another important factor was whether the journal was read by their community.

Over half the respondents thought that constructive peer review process was 'very important', and 80% thought that a fast editorial decision was either 'quite important' or 'very important'.

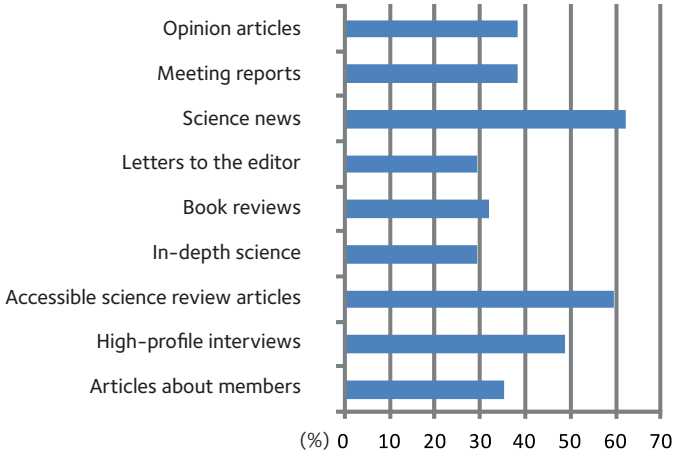
Impact Factor still influenced over half the people surveyed, although the reputation, reach and constructive peer review were considered more important.

Just over a quarter of respondents had published via 'Gold' Open Access routes, and over a third of these responses indicated publication in one of The Society's journals using the 'author-pays' route. Funding of Open Access payments came from their institution (33%) or via their grant funders. One-fifth of respondents have self-funded the open access charge.

We are encouraged to learn that over 70% of respondents welcomed the launch of our new Open Access journal, *Physiological Reports*.

In the future, *Physiology News* should publish more ...

(See Physiology Feed on page 7 for our new initiative on providing science news in the magazine).



Physiology News

96% of you read *Physiology News*. The majority prefer to skim each issue and select the best articles for your full attention.

16% read *Physiology News* cover-to-cover.

4% do not read *Physiology News*!

68.8% of you still prefer your *Physiology News* in print.

75.8% 'agreed' or 'strongly agreed' that the new format *Physiology News* (launched in Spring 2012) looks much better than the old format. 58.7% held it to be a more enjoyable read. 41.4% said it was more useful to them as a physiologist.

About The Society

70% 'agreed' or 'strongly agreed' that membership of The Society is increasingly valuable.

63.6% of respondents valued their Society membership for the networking opportunities it provides.

85.7% rated our membership services as 'good' or 'very good'.

The Society's events

58.2% of you have attended The Society's Main Meeting at least once in the last three years.

34% have attended one of The Society's Themed Meetings.

45% of those who have not attended a Society meeting in the last three years say that it is too expensive (we look forward to increased applications for travel grants!).

Congratulations to Stephen Town and Craig Sharp, who won iPad Minis in the Membership Survey prize draw. Stephen is an Affiliate Member working at University College London's Ear Institute. Craig is a retired Member based in Birmingham.

Craig said: "My very first job, in 1956, was as an Assistant Lecturer in Sir James Black's Department of Veterinary Physiology in Glasgow. I had a Chinese colleague there who used to say 'If heaven drops a date, open your mouth!' So, I will simply say a very warm 'thank you'!"

Women in Science at IUPS 2013

Caroline Wood

Volunteer at IUPS 2013

Despite a greater number of women taking up scientific careers in recent decades, there is still a notable female absence within the upper tiers of research. The reasons behind this discrepancy, besides the more general challenges facing women in science, were discussed in a lively series of lunchtime sessions at the IUPS 2013 congress in Birmingham, UK, this July. Each talk was attended by over 100 delegates, the rooms humming with animated conversation. This was clearly not a 'mother's meeting', however, due to the distinct undercurrent of seriousness as key concerns were brought forward. The sessions coincided with the launch of the IUPS booklet *Women in Science*, which carries profiles of distinguished female physiologists – copies of which were rapidly snapped up by delegates. The following are summaries of all three Women in Science sessions.

Session 1: Why mentoring and sponsorship works

Co-chair of the session Caroline McMillen, Vice Chancellor of the University of Newcastle, Australia, opened the debate by describing a Harvard Business Review survey of 4,000 business graduates which found that, over two years, the men achieved 15% more promotions despite the women receiving more mentorship. A key factor identified by the authors was that the males benefitted from more senior and influential mentors. The panel of speakers – including president of the Royal Swedish Academy of Sciences, Barbara Cannon – described how their careers had progressed thanks to (male and female) mentors who had taken an active interest in their development. Having an influential model prepared to speak up for them was a critical factor for each of these women's careers. This suggests that young women researchers should be more strategic about their choice of mentor, factoring in their seniority and influence, as well as research interests.

A key message was that women need to seek recognition for their work and engage with the research community in order to get their 'lucky break'. There was general agreement that greater funding opportunities to send young women researchers to conferences, as well as increased networking between senior scientists, could be an effective strategy. It was also suggested that women should make the effort to sit in on committee meetings or obtain panel positions; this can provide invaluable insight into 'the gendered nature of leadership' and how female candidates are perceived in interviews, compared with males. The structure of a committee panel, meanwhile, can influence the dynamics of an interview, and it was agreed that sponsors must be aware of these differences in order to train their mentees to modify their behaviour to communicate most effectively.

Concern was raised, however, that defined programmes of sponsorship may be detrimental. As Barbara Canon observed: "It is difficult to see how sponsorship could work if it is organised too much, because you have to believe in the person you are going to sponsor." Individual sponsorship can give great individual benefits, as demonstrated by the panel, yet this is clearly insufficient. Although most institutes run mentorship schemes, sponsorship is distinct in that it stems from a personal belief in the candidate's excellence. As Abigail Fowden, Professor of Perinatal Physiology at the University of Cambridge, said: "Sponsorship is something unique between sponsor and individual ... the only way you are going to be sponsored is by being good at what you do."

This sounds a call for female mentors to take a proactive role in promoting women candidates they genuinely believe to be excellent.

Left to right: Barbara Cannon, Lisa Nicholas and Abigail Fowden in the first session on mentorship

Session 2: Juggling Balls – family and physiology

The second session focused on the challenge of balancing active research with family commitments. A panel of six speakers, encompassing a wide range of career stages, family sizes and native cultures, gave their testimonies. It was clear that a combination of both personal resilience and external support had enabled these women to maintain distinguished scientific careers. Their examples illustrated how compromise can often begin right at the point of marriage: many had been obliged to disrupt their early careers by moving to where their husband could be most successful. On having children, some then had to struggle against an attitude that "if you can't manage your children, you shouldn't be in research".

The panel and audience agreed that a supportive partner, willing to take their share of the juggling, was critical. In addition, some mothers had benefited from a culture with close family structures, allowing grandparents to carry part of the childcare burden. For those without this option, external provision – in the form of crèches, local schools and before/after school clubs – can decide whether a mother can remain in research.

Rafidah Hanim Mokhtar described how the Malaysian school system was tailored for working women, with the school day ending as mothers finished work. Kathy Morgan, of Boston University, emphasised how getting help and learning to multi-task were vital priorities, asserting that "You can't hold down two full-time jobs, and research is a full-time job … if you compromise, you can't compete." Not everyone has the luxury of being able to delegate tasks to an administrative assistant, yet various strategies were discussed including encouraging teamwork and collaboration in the lab, not assigning projects to one person, establishing effective and flexible communication (such as email and Skype) and hosting regular lab meetings.

The session ended on a positive note, with the panel urging working mothers not to feel guilty, but rather to ensure that the time they spend with their children is of the highest quality. It was agreed that it needs to be possible for a woman to take a break from work to have a family, and that institutions can enable this by providing more part-time positions and childcare allowances. In this respect, a new initiative at Cambridge University is highly encouraging: a sum of money (£10-20,000) will be made available to every mother returning from maternity leave to fund whatever activity will most help in the transition back to work.

Session 3: What glass ceiling?

The final session explored the concept of the 'glass ceiling' as an invisible barrier against success, and the degree to which this applies to female researchers. Using her own progression as an example, Bridget Lumb asserted that this idea is not helpful for women, as it predisposes them to believe that obstructions are inevitable due to their gender, when, in reality, everybody comes across hurdles in their career. She described how her initial reluctance to apply for leadership positions changed with the realisation that men are encouraged to put themselves forward when they meet most of the job criteria, whereas women are put off by their weaknesses, even if they are just as capable. This idea is explored further in the book *Beyond the Boy's Club*.

Dame Nancy Rothwell, President and Vice-Chancellor of the University of Manchester, discussed if there is a glass ceiling or 'hurdles in the labyrinth'. She advised to "be true to your own strengths" and "listen to your head, but follow your heart."

It was clear from the range of speakers and audience contributions that female researchers are more likely to progress if they are unaware of the 'glass ceiling', suggesting that this barrier is imposed in part by women themselves. This was illustrated by Ana Abdala, of the University of Bristol, who described a comprehensive study of research funding allocation commissioned by the EU. This found that women tended to apply for fewer grants and for smaller amounts of money, yet were just as successful (if not more so) as men in most European countries.

There was discussion around training women to demonstrate greater confidence in interviews. Having more females on funding panels was also identified as a future strategy for progress. Although things appear to be moving in the right direction, there is no room for complacency: as Ole Peterson summarised: "The glass ceiling is definitely not complete, it's patchy. But it does exist." The overriding message was that smashing the glass ceiling begins first in the woman scientist's own mind.

Each session was imbued with a positive atmosphere, with many attendees stating that they had been 'empowered' by meeting women who had demonstrated that it is possible for females to have a successful research career. There was a feeling that, had the rooms not been booked for afternoon symposia, many attendees would have remained to network further and share experiences. There were considerable calls for similar sessions and a review of progress to be held at the 2017 conference in Rio de Janeiro. If the strategies discussed at IUPS 2013 are acted upon, there is every possibility that encouraging changes will have taken place by this time.

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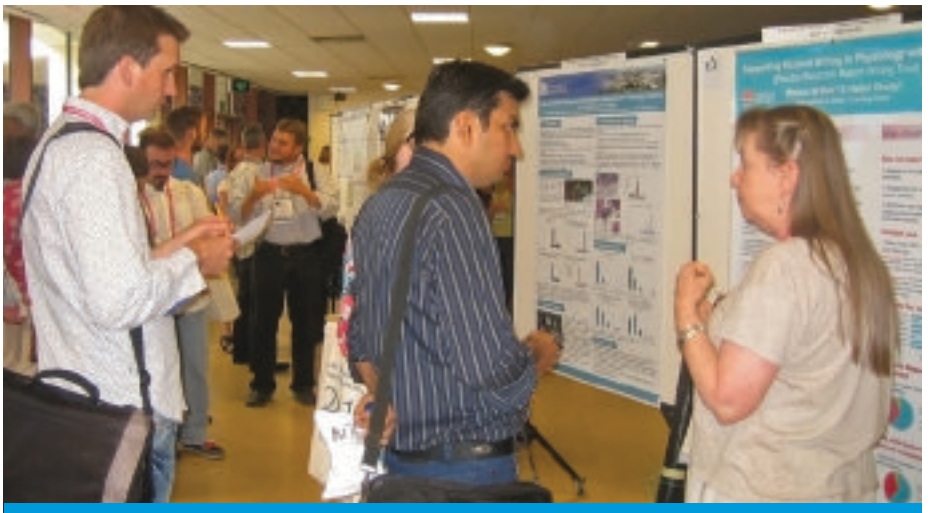
The Society's Education and Teaching (ET) Theme: What is it and what does it do?



Poster session at the 2013 IUPS Teaching Workshop

Judy Harris
University of Bristol, UK

The ET Theme is one of the seven 'themes' that all Physiological Society Members can join. It evolved from the Teaching Special Interest Group (SIG) for which I took on the role of co-convenor, along with Richard Helyer, in 2007. At that time we were keen for the Teaching SIG to contribute to raising the profile of education within The Society and we also wanted to extend the SIG's remit and membership. Since virtually all physiology academics teach in some shape or form we felt that it should have something to offer a wide range of Members. Interestingly, in other societies such as the APS, FEPS and IUPS, education tends to have a much higher profile than was the case for PhySoc in 2007.

So, has the profile of education within The Society increased in the last six years, and has the ET Theme played a part in this? I hope and believe that both are true!

ET Theme membership has grown from just over 100 in 2007 to nearly 550, but we remain keen to recruit Members, especially those on traditional 'three-legged' (research, teaching and administration) contracts. All Theme Members receive a regular online newsletter outlining on-going developments, upcoming events and funding opportunities. The budget that we receive from the Education and Outreach Committee is used in a variety of ways to benefit Members.

Since 2007 we have supported five regional teaching workshops in London, Manchester, Birmingham, Bristol and Belfast, with another planned for Dundee in 2014. Funding is used to provide travel grants for participants and speakers as well as contributing to room hire and refreshments. In addition to providing opportunities to share good teaching practice, these events facilitate the creation of regional physiology teaching networks, which can be especially helpful for Members who are not part of a strong physiology teaching community within their own university – a situation that is becoming more common.

Recently the Theme supported the IUPS Teaching Workshop in Bristol by providing poster prizes, as well as travel grants for several overseas delegates. The latter made it possible for physiologists from developing countries to attend an international teaching event which not only promoted mutually beneficial exchanges about teaching in different countries but also helped to create and foster links across a global physiology teaching community.

The ET Theme also hosts an Education Symposium at every Physiological Society Main Meeting. Before 2008, these were scheduled immediately before the Main Meeting but attendance tended to be poor. They now run in parallel with the research symposia and attendance has increased significantly. Topics have included practical physiology teaching, final year research projects, sustainability of physiology teaching and methods for setting the pass mark in examinations – a General Medical Council requirement for all medical assessments, now being adopted by several other degree programmes. Some Education Symposia have included the Otto Hutter Physiology Teaching Prize Annual Lecture, another recent initiative within The Society that has raised the profile of education.

An informal lunchtime teaching discussion has also become a regular feature of each Main Meeting. These focus on topical issues such as development of The Society's core physiology curriculum for medical training and the valuation/status of teaching in career progression.

The latter is an issue close to my heart and the ET Theme has been able to make a significant contribution to national debate in this area through collecting data via membership surveys on reward and recognition for teaching in higher education. We are now working closely with the Academy of Medical Sciences, the Society of Biology and the Higher Education Academy to promote an integrated approach across the higher education sector in raising the profile of, and recognition for, teaching activities in career progression for all academics, not only teaching specialists.

After six rewarding years as co-convenor, since 2010 with Dave Lewis, it's time for me to hang up my ET Theme convenor boots. In some ways I'm reluctant to do this because it's an exciting time for education within The Society but fresh blood is always welcome. There will be an online election for my successor. More information will be circulated soon but if you're interested in putting your name forward, please let Dave Lewis, Chrissy Stokes or myself know. Also, feel free to contact any of us if you would like more information about the role, or contact Chrissy if you would like to join the ET Theme.

Finally, I would like to thank Rich and Dave for their input as successive co-convenors, the Education and Outreach Committee for provision of the ET Theme budget and Chrissy for her invaluable support within the Theme over the last six years.

2013 *Forthcoming events*

10–13 Nov

Journal of Physiology at Neuroscience 2013
San Diego, USA
Booth 122
www.sfn.org/annual-meeting/neuroscience-2013

17–19 Nov

Journal of Physiology at American Heart Association
Dallas, USA
Booth 426
www.scientificsessions.org

10 Dec

Early-Career Physiologists Symposium
New Insights into Ion Transport Physiology
Royal College of Surgeons in Ireland, Dublin
www.ecps2013.blogspot.ie

11–13 Dec

Epithelia and Smooth Muscle Interactions in Health and Disease
Joint EM and VS Themed Meeting
The Convention Centre, Dublin, Ireland
www.physoc.org/emvs13

Meeting Notes

The road to IUPS

21–26 July 2013, International Convention Centre, Birmingham, UK

David Eisner
University of Manchester, UK

Bridget Lumb
University of Bristol, UK

Rapt audience in main auditorium

In 2004 IUPS put out a call for bids to hold the 2013 Congress. At that time we were both on The Physiological Society's Executive Committee as Meetings Secretary (BL) and International Secretary (DE). The Society had just changed the way its own meetings were organized, moving from seven or eight meetings per year to one larger Annual Meeting. It had also reorganized its administration with a professional office staff. In an optimistic moment we therefore thought that if we could organize an Annual Meeting of 1000 attendees, could it really be much more difficult to scale up to IUPS?

The then Executive Committee was enthusiastic. DE and the then President (Alan North) presented our bid at the 2005 meeting in San Diego. Compared to the many glitzy presentations we have seen since, with superior graphics and videos, it was rather austere and amateurish, but it obviously did the job. Having won the bid there then ensued a feeling of "be careful what you wish for, as you may get it". We alternated between being, on the one hand, terrified by the magnitude of the organizational task and, on the other, feeling that 2013 was in the infinite future and could be ignored in favour of more immediate matters.

The subsequent smooth running of the preparations for the meeting was due to two groups of people. Firstly, the Executive of The Physiological Society. In point of fact there were several changes in the composition of the Executive as various officers reached the end of their tenures and were replaced by others. What they all had in common was the desire to support the IUPS adventure but leave us and the IUPS2013 Organizing Committee free to design the congress. In hindsight, one of the most important decisions was made at the time of the original bid: the Organizing Committee was set up to contain two groups of members. One was unchanged throughout and contained those (including us) who were involved in the original bid and the other rotated and was made up of the President, Vice-President, Meetings Secretary and Treasurer of The Society. This led to almost seamless organization and made sure that the Congress organization was always well-integrated with The Society. The other group, without which the meeting would have been much less successful, comprised the highly enthusiastic and dynamic Society

Events Team led by Nick Boross-Toby. Nick did a wonderful job and, on a good day, even listened to us!

The first task was to fix the venue. We toured various congress centres and finally settled on the ICC in Birmingham. One of the main advantages of the ICC is that it is very centrally located, close to the canalside restaurants, bars and cafes. There is also ample hotel accommodation nearby. The choice of Birmingham was vindicated by the number of IUPS attendees we saw sitting outside enjoying informal interactions.

David Eisner presents the FEPS Lecture prize to Juleen Zierath of the Karolinska Institutet, Sweden

From the very beginning, we had hoped to involve other European Societies in the organization of IUPS 2013. The Federation of European Physiological Societies and the Scandinavian Physiological Society both made IUPS 2013 their annual meeting. Unfortunately our attempts to encourage the German Physiological Society (the other large, European, national society) to hold their annual meeting at IUPS did not succeed. A brighter outlook materialized, however, when Ulrich Pohl approached us with the suggestion that two vascular societies (the European Society for Microcirculation and the European Vascular Biology Association) were due to meet in 2013 and how would we feel about them meeting at IUPS? That was a 'no brainer' and a stimulating scientific collaboration was born providing a real strength in the final programme.

The next task was to select the science to fill the meeting with. This was done by an International Scientific Programme Committee (ISPC), chaired by DE with Walter Boron (IUPS Secretary General) as co-Chair. The Committee itself was made up of representatives from the IUPS Council as well as those selected from The Physiological Society and elsewhere in Europe. We first selected 33 keynote and plenary lecturers. Particular effort was made to ensure that these speakers were reasonably well-balanced for both their geographical origins and their gender. In the end, 10 out of 33 keynote speakers were female, a fraction which compares very favourably with most other meetings. Gender related issues had a major airing in the eventual IUPS meeting with three lunchtime sessions (organized by Susan Wray) dealing with various career stages.

We put out a call to the international physiology community for suggestions for symposia to fill the 100 or so available slots and were gratified to receive 350 proposals. This enthusiastic response made a lot of work for the ISPC. Although some of the initial work was done by email, the bulk was done at a two day meeting in Birmingham in early March 2012. The IPSC members worked hard to select and, in most cases, combine symposia. The final symposia had 294 male and 204 female speakers. Credit for the efficient development of the programme must go to Anne King, David Thwaites, Andrew Trafford and Susan Wray who each took responsibility for part of the programme. This involved much negotiation with symposium organizers and, in some cases, finding replacement speakers.

It almost seemed unreal when we arrived in Birmingham on Saturday 20 July. For so long

Walter Boron presents a PhySoc prize to Denis Noble to mark his President's Lecture

Bridget Lumb of the IUPS2013 Organizing Committee speaks at the Closing Ceremony

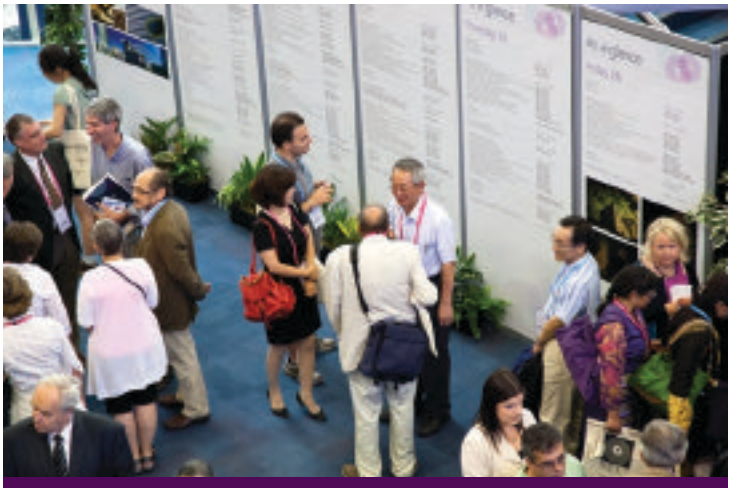
the IUPS meeting was a very distant thought. It is up to others to judge the success of the meeting. All we can say is that we thoroughly enjoyed it. It was very stimulating to be able to listen to some extraordinarily good keynote and plenary lectures as well as symposia, and to meet old friends and make new ones.

We would like to end with a reflection on the future of IUPS meetings. The local and international committees for IUPS2013 assembled a motivated and committed team that ensured a highly successful meeting which brought together a worldwide community of physiologists. Increasingly, international scientific meetings specialise and focus on particular aspects of our science. What sets IUPS meetings apart is that they bring together many different disciplines and allow cross fertilisation of thought and interest. Working with our Brazilian colleagues we are confident that IUPS2017 in Rio de Janeiro will build on our experience and produce an even better platform for the dissemination of physiological science.

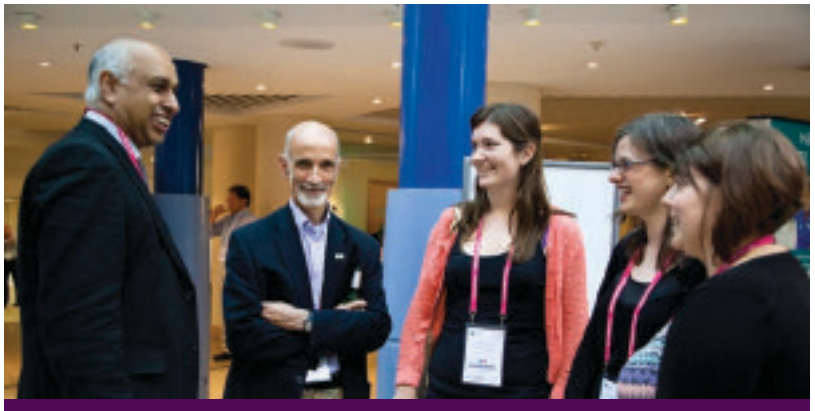
Russell Foster delivering the Public Lecture 'Rhythms of life'

The Mall of The ICC

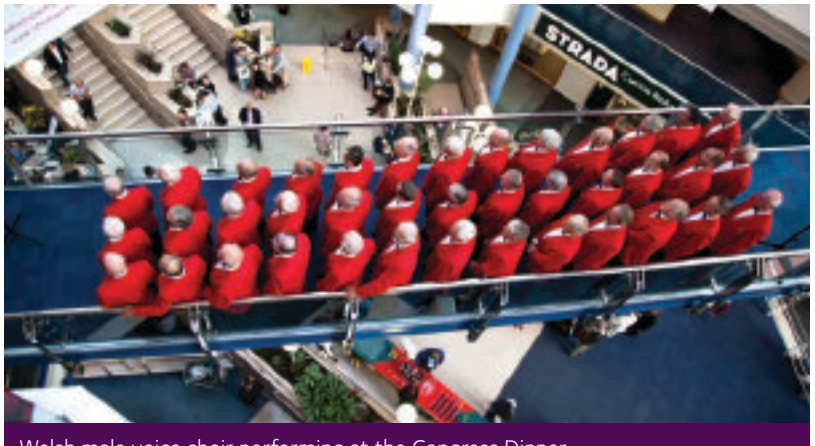
Mike Collis and Rod Dimaline at the Congress Dinner



Networking between sessions at IUPS 2013



The Society's Prem Kumar and President Jonathan Ashmore talk to delegates



Welsh male voice choir performing at the Congress Dinner

Cormac Taylor of GI Distress and the Fabulous FASEBettes at the welcome reception

Chief Executive Philip Wright, Meetings Secretary David Wylie and Past President Mike Spyer

Physiologists enjoyed dancing to Irish band 'Beer for Breakfast'

Over 1700 posters were presented at IUPS 2013

The Society's Jennie Wallace and Casey Early chat with Ian McGrath at The Society stand

Staff celebrating a job well done!

Student impressions of IUPS 2013

Bryn Savill

Cardiff University, UK

I arrived in Birmingham for the IUPS meeting, having had my poster abstract accepted many months before, and had little idea what was ahead having been swamped by my final medical examinations for the previous two months. This year I've organised two national conferences, and attended several sport and exercise medicine meetings (my research interest), so I thought I knew what went into producing conferences similar to this! Nevertheless, I was staggered by the sheer size of the event (it's the biggest conference I've ever been to by a long way!) and with every last detail cared for – I cannot even imagine the level of organisation that must have gone into it. Each day The ICC was filled to the brim and there was a buzz from the expectant delegates awaiting the physiological feast on offer. The academia on display was in an area that I wasn't overly familiar with and it was clearly way above that which I had encountered before, but it proved to inspire and prompt me into looking further into areas which I hadn't explored before.

The biggest surprise of the conference for me, however, was the poster presentation sessions. The sessions, held in their own slot in the evening, were jam-packed with delegates discussing the latest research in the field. This was a refreshing change to what I had previously experienced at other meetings, where poster sessions were crammed into lunch with only the judges really paying any attention to them. As such, I found it a highly rewarding experience. My research was critiqued and questioned by leading academics, even more so than when I had entered posters into competitions at other conferences, whilst the discussions also provided me with new research ideas and angles. It was such an inspiration to be surrounded by this breeding ground for new research that I will certainly be trying to make the trip to Rio in 2017 with some new research! I would like to thank The Physiological Society for this fantastic opportunity to attend and present at this prestigious event.

IUPS: What was said ...

"If physiology has moved off centre stage, it is coming back with a vengeance"

Denis Noble President of IUPS

"A great and unforgettable meeting, with an atmosphere of friendship and collaboration"

Benedito H Machado Organising Committee for Rio 2017

"It's very unusual to have eleven different symposia at once and lots of choices to go to, I didn't expect that at all. It's very organised and the staff have been very helpful"

Surawee Chuaiphichai University of Oxford

"It's been very interesting. The lecture on Monday on circadian rhythms was very clear, very accessible, not just for professionals"

Ksenija Cankas University of Ljubljana

"It's been an eye opener, especially the Women in Science sessions. Women go through a lot, we all have common challenges"

Oyelowo Oluwakemi T University of Lagos

"It's an exciting place to be because of the number and variety of physiologists here. I really enjoyed my poster session because I got a lot of excellent feedback and encouragement"

Serena Cerritelli University of Bristol

"What I found the best was that I could attend talks not necessarily about what I'm studying. I really enjoyed the keynote lecture on fish and global warming because it is not something I am normally interested in. Just fascinating"

Gosia Furmanik King's College London

IUPS proceedings abstracts available online

Please view or download from The Society's proceedings abstracts archive at
www.physoc.org/proceedings/issues

IUPS 2013 lectures

See lectures from IUPS 2013 online at
www.physoc.org/iups2013_lectures

Meeting Notes

IUPS and ADInstruments Teaching Workshop

18–21 July 2013
University of Bristol, UK

Penny Hansen

Co-chair of the IUPS Education Committee, Memorial University, Newfoundland, Canada.

Although English was the language of this 8th Teaching Workshop associated with an IUPS Congress, I could hear many other languages, such as Arabic, Spanish, Chinese and Swahili, being spoken as colleagues from 28 different countries chatted and discussed physiology with new and old friends during poster sessions and refreshment breaks. This cultural diversity was enhanced during the farewell party on the last evening of the workshop when we all wore clothing to reflect our countries or ethnic backgrounds – everything from Japanese yukata kimonos to African dashikis and Indian saris to my plain old Canadian red and white maple-leafed T-shirt.

The Congress was hosted by the modern University of Bristol set amidst the beautiful old buildings of this 16th century city. The local organizing team, headed by Judy Harris, had thoughtfully attended to every detail and answered every emailed question so that all arrangements for us went smoothly and efficiently. One hundred and nine physiologists arrived by airplane, bus and train from six continents for four days of intense discussion and work. Looking around I saw approximately equal numbers of men and women of all ages, well-distributed from students up to the most senior physiologists, such as Olusoga Sofola from Nigeria and Osamu Matsuo from Japan.

The Workshop was titled 'Tune up your Teaching: Trends, Tips and Tasters'. The International Programme Committee, co-chaired by Robert Carroll and Jonathan Kibble, had created a full schedule of five plenary and five short talks, 18 parallel small-group workshops, and daily poster sessions. We learned about such trends as simulation, role of mobile devices, team-based learning, and relating laboratory data acquisition to patient cases. Tips included, for example, ways to use self-assessment, to organize regional workshops, and to get your educational research published. A plethora of nearly 50 posters acted as intriguing tasters illustrating the broad range of innovations and educational scholarship being carried out by physiology teachers around the world.

The Education Committee of IUPS has had responsibility for organizing these satellite Workshops since the first one, held in Jenolan, Australia, in 1986. ADInstruments Company generously funded each of these workshops, keeping costs to participants extremely low and pro-rated according to the World Bank classification of countries by per capita income. The Bristol workshop received additional generous sponsorship from The Physiological Society and Wiley (amongst others). Part of this funding enabled the award of five poster prizes selected by a small judging panel, who agreed that the quality of the posters – the scope of which encompassed virtually all of the countries represented at the workshop – was very high. As has become tradition, participants who

were at each of the preceding workshops posed for group photos. Sadly there was only one person present, Adrianta Surjadhana, who has attended all of the workshops. He also initiated and manages the IUPS teaching listserv at iups-teaching@yahoogroups.com, so that physiology teachers around the world can keep in touch by exchanging information and news.

A report documenting these and other IUPS workshops can be accessed from the IUPS website at www.IUPS.org. We chatted about our rich memories of each workshop – I remember very well the bear tracks through our camp in the overnight snow at Pali Mountain, the rustic venue in a beautiful northern forest of Russia, explaining our posters to the Princess Royal in Inverness... Perhaps my strongest memories of Bristol will be the heat wave that enveloped England while we were there, but especially the moment at the end of the farewell party when everyone joined hands in a circle and sang Auld Lang Syne. These and other regional IUPS-sponsored workshops that bring physiologists together are important not only for mutual sharing of educational innovations and research, but perhaps even more so for maintaining the spirit of community support so vital for colleagues who are often geographically isolated and working in resource-poor regions.

Meeting Notes

International Early-Career Symposium (IECS)

20 July 2013
University of Birmingham, UK

Emma Thompson

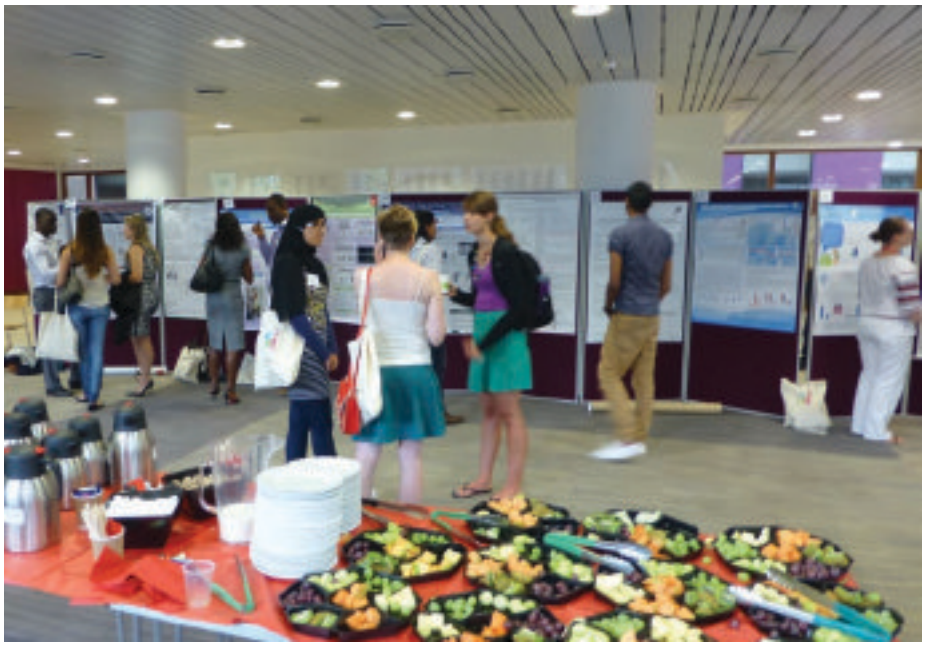
University of Birmingham, UK

IECS ran as a satellite to IUPS 2013 and was organised by an international committee of early-career physiologists. The theme of the meeting was 'Clinical and Translational Physiology', and we aimed to integrate basic physiological research with resulting therapeutic applications. To this end we ran three focused sessions, 'Cellular and Neurophysiology', 'Cardiovascular and Respiratory Physiology' and 'Endocrinology and Metabolism in Health and Disease', and included talks presenting results from *in vitro* experiments through to application in humans within each.

We welcomed over 70 delegates from around the world, and they provided us with 16 outstanding talks and over 40 poster presentations. The standard was extremely high and our congratulations go to the prize-winners: Juliana Angheben (Federal University of São Paulo) for Best Oral Presentation; Anusha Seneviratne (Imperial College London) for Best Poster Presentation; and Dominika Bijos (University of Bristol) for Best Scientific Image.

As well as the impressive contributions from our delegates, we were very pleased to welcome two world-renowned keynote speakers, Michael Joyner (Mayo Clinic) who gave a talk entitled 'Physiology and the Future Oversimplified', and Mark Hanson (University of Southampton) who spoke on 'Why Physiology is Needed to Meet the Post-2015 Global Health Challenge'.

We also ran four interactive workshop sessions on issues important and relevant to early-career scientists, 'Career Development and Opportunities Overseas' (Richard Wainford, Boston University), 'Statistics and Study Design' (Gordon Drummond, University of Edinburgh), 'Scientific Writing and Getting



"It was a great experience! It provided ample opportunity to relate to and interact with peers from different parts of the world"

Published' (David Sheppard, University of Bristol) and 'Scientific Outreach' (Sarah Chapple and Aisah Aubdool, King's College London).

Throughout all of the sessions there were great questions and interaction from the audience, as well as from a number of our invited academics. This created a relaxed and friendly atmosphere and allowed for exciting scientific discussion and exchange of ideas. We also had a drinks reception and evening social event, giving further time for networking as well as a brilliant quiz which included a physiology picture round!

The day would not have been possible without the generosity and support of our sponsors; The Physiological Society, The University of Birmingham's Centre for Learning and Academic Development, Integrated DNA Technologies, Abcam and New England Biolabs. Special thanks go to Don Whitley Scientific who brought a wonderful display as well as wine and cheese!

As a member of the organising committee I would like to extend my sincere thanks to The Physiological Society for the opportunity, my fellow committee members who worked so hard to make the day run smoothly and to all those who attended. I hope these events will continue to take place to encourage and aid the development of early-career physiologists. This will be key if, as Denis Noble said in his IUPS opening address, physiology is to move back onto centre stage.

"This was a great and extremely innovative meeting with the view of empowering early-career researchers with useful information and an environment in which to grow"

The IECS 2013 Committee. Left to right: Adebayo Adebisi (student helper, University of Birmingham, UK), Sarah Chapple (King's College London, UK), Rosalind Cook (University of Otago, NZ), Emma Thompson (University of Birmingham, UK), Catherine Dunford (University of Bristol, UK), Abubacarr Gassama, Keith Pugh and Rehan Talib Junejo (University of Birmingham, UK). (Missing from photo: Daniel B. Zoccal (Sao Paulo State University, Brazil) and Paloma Alonso-Magdalena (University Miguel Hernandez, Spain).)

THE SCIENCE OF LIFE

How your body works

Competition for 16-19 year-olds

This is your chance to design and conduct your own research project in any area of physiology, and then present your findings to scientists at a major scientific conference in London during the summer of 2014

www.understanding-life.org

Help us spread the word

If you have contacts with any 16-19 year-olds, please tell them about this competition. We're hoping for lots of fantastic entries this year!

Mentors needed

We are looking for researchers at any stage of their career to mentor the students taking part in this competition. If you're interested, please email education@physoc.org

The Science of Life
How your body works

The Physiological Society

How drugs are discovered and developed

The risks and the stakes are high in developing novel pharmaceuticals. The demands of scientific rigour, safety and regulation all add up to a decade-long commitment with no guarantee that it will pay off for patients or investors. What is the route from research discovery to market and what obstacles do candidate drugs come up against?

Michael Collis
Editor, Physiological News

Modern drugs have revolutionised our lives and our health. The pharmaceutical and biotechnology companies responsible for these drugs invest large sums to discover and develop new therapies. The risks of failure are, however, very high. A new drug with a mechanism of action that has not been previously evaluated in man has about a 1% chance of reaching the market. Even drugs that are improvements on clinically proven therapies only have about a 10% chance of success. The failure of mechanistically novel drugs is usually due to a lack of sufficient efficacy in treating the target disease (i.e. the original hypothesis on which the new drug was based turns out to be wrong or only partially correct). Problems with absorption/metabolism or unexpected side-effects in man are further pitfalls that can afflict both novel and clinically precedented drugs stopping their development. It is hardly surprising that the pharmaceutical industry is continually investigating more efficient ways to operate and better ways to predict which new drug approaches have the best chance of being both efficacious and safe. Despite this, the industry is going through a major consolidation with many mergers and takeovers with the unfortunate result that overall research capacity is reducing. The process of discovering and developing new drugs is continually evolving. In this article I will describe the process using small molecule pharmaceuticals as the example (Fig. 1). Potential biological treatments – antibodies, therapeutic proteins and genetic therapies – go

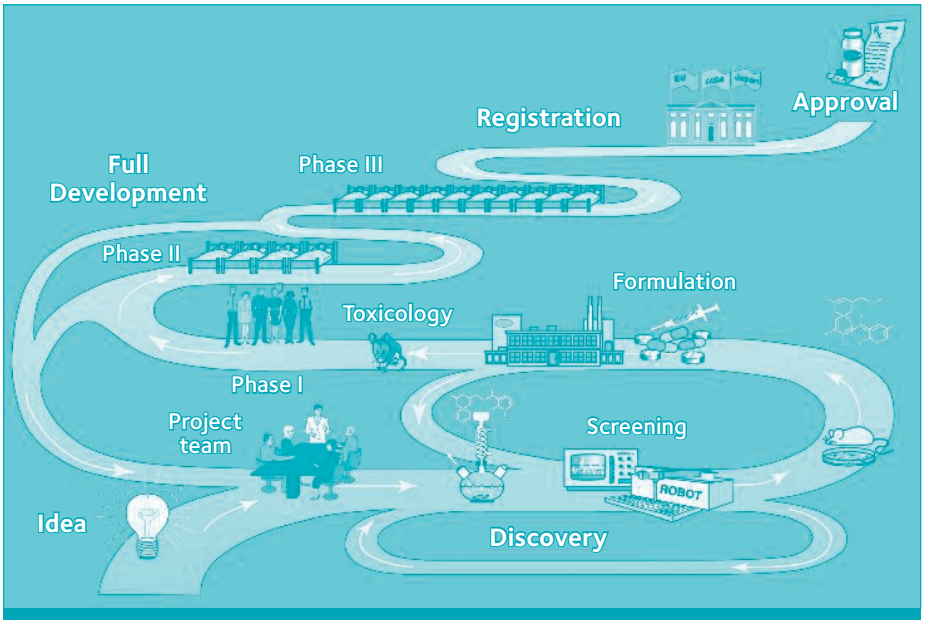


Figure 1: Schematic of the route from the idea for a new drug to its approval for marketing

"A new drug with a mechanism of action that has not been previously evaluated in man has about a 1% chance of reaching the market."

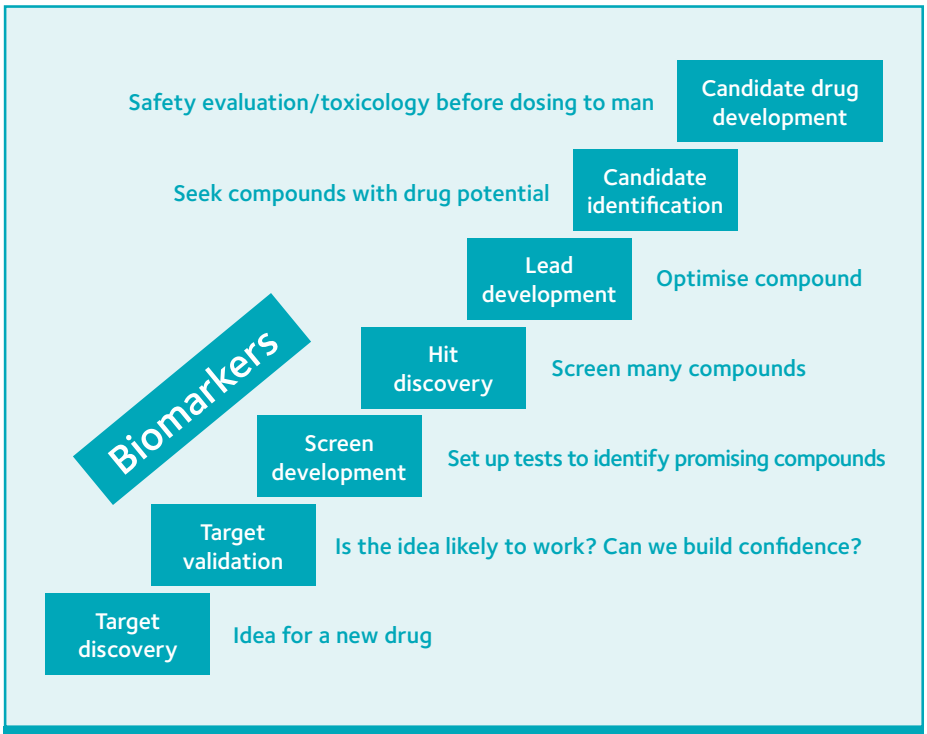


Figure 2: Schematic of the stages from idea to a candidate drug entering development

through similar development processes, although the earlier research stages of selecting and optimising the best candidate drug will have specific tests based on the characteristics of the biological agent that is sought.

The initial idea that a chemical compound interacting with a particular biological protein (drug target) may be useful in the treatment of an important disease usually arises from a synthesis of published academic research, disease knowledge (including genetic information) and in-house research in the pharmaceutical or biotechnology company. Certain drug targets with discrete high affinity binding sites are amenable to interaction with low molecular weight (<500) compounds, e.g. ion channels, G-protein coupled receptors and certain classes of enzyme. Protein targets with diffuse low affinity binding sites are more likely to interact with large biological molecules than with low molecular weight chemicals. Once the idea for a new drug approach has been formulated and reviewed in a company, a research team is formed to evaluate the potential for this mechanistic approach to have efficacy in the disease of interest and to be safe. This early target validation stage (Fig. 2) utilises published knowledge on the drug target and wherever possible involves experiments to evaluate the effects of interacting with it. To do this the project team need a compound with some affinity for the target, or an anti-sense or transgenic approach to allow them to investigate the effects of stimulating or inhibiting/deleting the target *in vivo*. Having an 'animal model' of the relevant disease with predictive power regarding efficacy in man is extremely valuable at this stage. In some disease areas, such as mental health disorders, the lack of animal models that mimic some of the symptoms of disease and that have predictive power is a major impediment that prevents many companies from seeking new drugs for these complex and important disorders. As well as evaluating the potential efficacy of a new therapeutic approach, the project team will investigate what side-effects are likely to be associated with its mechanism of action and whether these would be acceptable to patients.

The next stage is to develop biological assays (screens) to identify compounds that interact with the drug target (screen development, Fig. 2). These assays (typically enzyme inhibition or receptor/channel binding) invariably use the human protein (target) of interest and are operated *in vitro* at very high throughput (many thousands of compounds a day) using robotics and minute reaction volumes (Fig. 3). The nanotechnology used in high-throughput drug screening is highly specialised as are the scientists who develop and run these assays. New chemical compounds and those already stored in the company collection are screened with the aim of identifying compounds referred to as 'hits' that bind to the drug target with micromolar affinity (Fig. 2). The synthetic chemists in the company subsequently modify the hits, usually aided by structural information on the drug target, to develop compounds known as 'leads' that bind with nanomolar affinity. Leads are further modified to optimise their affinity for the drug target and to reduce

Figure 3: High throughput screening using robotics and nano-well plates

affinity for closely related members of the target protein family. Drugs need to have high affinity for the target, but they also need to be selective for that target. If they also bind to other enzymes, receptors or ion channels related to the target they are likely to cause unwanted side-effects. Further testing of leads in cell-based assays is then used to ensure that they have the desired effect in intact cells as well as in the test tube.

A chemical compound that has high affinity and selectivity for a drug target in *in vitro* assays is not a candidate drug. Drugs need to be absorbed by an acceptable route into the patient's body and to maintain an effective concentration in the biological effect compartment for an appropriate period – usually 12–24 hours. There is often a fine balancing act to be mastered by the medicinal chemist between optimising the desirable properties of high affinity, selectivity and good absorption and slow metabolism *in vivo* for a candidate drug. The resulting candidate drug is usually a compromise between these properties. Once a candidate drug has been identified, it will undergo safety evaluation (safety pharmacology) to identify any unexpected adverse effects on major body systems such as the cardiovascular and nervous system.

An important activity during the early stages of the drug discovery process is identification of a biomarker of drug activity that can be used in man. Amazing as it may seem, in the past many drugs were given to patients without a clear idea of what dose was needed to have the desired biological effect. This meant that a negative result in a clinical trial provided no useful information, as it was impossible to determine whether lack of effect was because the mechanistic approach was wrong or because the dose was wrong. Nowadays companies want to identify a biological marker that can demonstrate in man that the drug is having the expected biological effect, before tests in patients are started to evaluate whether this effect is beneficial in treating the disease. If, for example, the drug inhibits an enzyme, then a biomarker might be the accumulation of the substrate for this enzyme. Only when the biomarker shows the new drug is having its expected biological action in human volunteers will the company go into clinical trials in patients.

But before the drug can be given to healthy or ill humans, toxicology studies must be performed (Fig. 1). These are designed to identify the dose (or *in vivo* concentration) of a new drug that causes detectable toxic effects. To do this, doses of the potential drug are increased stepwise in two species of experimental animals. Once the minimum toxic dose is known, it can be compared with the predicted therapeutic dose to decide whether the drug has a sufficient margin of safety to be given to humans. All drugs have adverse effects at some dose, but there is no fixed safety margin that must be achieved. The acceptable safety margin (therapeutic index) for a new drug depends on the medical scenario in which it will be used – a narrow safety window may be acceptable for an acute treatment for a life-threatening disorder for which there is no current therapy, a much

"The costs of drug discovery and development are huge, in the region of $1 billion for each drug reaching the market."

greater safety window will be required for less serious diseases and those where there are already treatments available.

Once the candidate drug has been shown to have an acceptable therapeutic index it can be administered to man for the first time in Phase I volunteer studies (Fig. 1). These studies in normal individuals involve administration of very low doses to assess the absorption and metabolism of the compound, ensuring that it can reach the effective concentration by an appropriate route and persist for long enough to allow an acceptable dosing regimen. This is where a biomarker of the drug's activity is so important as it will allow the scientist to define the relationship between the dose of drug, its plasma concentration and its biological effect and will define the dose to be used in the first patient studies. Phase I volunteer studies can also reveal subtle side-effects that could not be observed in safety pharmacology or toxicology studies in animals. Occasionally this reveals a potentially very useful unexpected effect of the drug. Remember that Viagra was designed for heart disease (by increasing cyclic GMP levels causing coronary vasodilatation and inhibiting platelet aggregation), but its interesting and important effects on male erectile function were identified in Phase I volunteer studies. (Further volunteer studies involved the use of instruments such as the 'rigiscan' and 'top shelf' visual stimulation – but that is another story!)

The next stage in the development process sees the new drug being given to patients in Phase II clinical trials. These clinical studies are designed and powered to answer the question, does this new drug benefit the patient? Phase II studies are usually conducted at a small number of specialist clinical centres using carefully selected patients to provide a relatively homogeneous group to allow efficacy to be evaluated using small groups (circa 100 per treatment group). If the new drug shows significant activity in the phase II trials (clinical proof of concept), then the decision will be made whether this is sufficient to progress into phase III clinical studies.

Phase III clinical trials tend to be worldwide and can involve from 3000 to 5000 patients. They are very expensive and pharmaceutical and biotechnology companies are very careful when deciding which potential new drugs are progressed to this stage. If a drug fails in phase III, perhaps because of a side-effect not seen in the smaller phase II studies, it is extremely bad news for the sponsoring company, which will have spent a great deal of money on it by this stage. Phase III clinical trials build a large database of evidence for efficacy and safety for a new drug. They also allow evaluation in different patient groups and different ethnicities and comparison with existing 'best care' therapy. If a new drug doesn't have a clear advantage over the existing therapies, then it isn't going to be successful and isn't worth progressing.

Accumulating an enormous amount of pre-clinical and clinical information about a new drug isn't the end of the discovery and development process. All of this data has to be submitted to the government regulatory authorities, e.g. the FDA, who approve the marketing of new drugs. The regulators scrutinise all the data the company have submitted and often ask for further studies to be performed. The path of drug discovery and development isn't linear; there is much potential for having to repeat steps and initiate new studies or even ditch the original compound and progress a different one. After a period of review and evaluation by the regulatory bodies (which can take up to two years) the sponsoring company may finally get approval to market the new drug for a particular disease and at a specified dose range. Over 10 years will have passed from the initiation of the programme – drug discoverers need a lot of patience. If an industrial scientist is involved with one drug in his/her lifetime that goes through the whole discovery and development process and reaches the market, he or she has done well. The costs of drug discovery and development are huge, in the region of $1 billion for each drug reaching the market. The patience, the hard work and the financial investment are justified if patients benefit from a new drug that gives them a better quality and/or length of life. If the company that discovered and developed the drug makes sufficient income from its sales, it can re-invest it in new drug discovery programmes.

How the pharmaceutical industry is changing

The pharmaceutical industry is changing its approach to discovering new drugs. Blockbuster, personalized medicine, or none of the above?

Raymond G Hill

Department of Medicine
Imperial College London, UK

Over the last 50 years many models have been proposed as the ideal way to discover drugs, but there is now general cynicism about the possibility of there being an optimal approach (Douglas *et al.* 2010; DiMassi & Foden, 2011). The cyclical nature of drug discovery caused by the time lag in incorporation of new academic basic science discoveries into drug discovery paradigms is as likely to have been the reason for swings from success to failure as is an inappropriate approach taken by the industry. Those who have worked in the pharmaceutical industry for any length of time will be aware that one constant factor for the sector is change. A continual process of internal reorganisation is a feature of the R&D organisations of most major companies. They seem to oscillate between a benevolent autocracy where a strong individual as R&D Director makes most of the key decisions swiftly (right or wrong) and governance by committee where decisions are delayed or not made at all. Surprisingly, both systems have been successful in the past and both have been shown to fail! In the golden years for the industry (probably dating from the mid-1980s to the mid-1990s) drug discovery seemed relatively simple, regulatory hurdles were easily jumped and governments and insurers were prepared to pay a premium for new and effective medicines. This resulted in large profits, some of which were reinvested in new research institutes and expansion of existing facilities. For example, over this period staff numbers in Merck/MSD R&D increased from 1500 to 10,000. There was confidence that application of modern automated technology such as robotic high-throughput screening would lead to yet more and better drugs. In the early years of this century it became obvious that just doing more of what had been successful in the past was not working and that a new approach was needed. Much more money was being spent on R&D without any obvious increase in productivity and this clearly could not continue (Munos, 2009). It was not immediately obvious what the new approach needed to be. Although an increase in collaborative research through links with academic laboratories and small companies was tried by all of the major companies, it did not seem to make an immediate difference to the number of new products reaching the market (Arrowsmith, 2011). However, a number of factors have become apparent in the recent past that will change our world in ways which we probably could not have guessed at 10 years ago. The belief that drug discovery could be industrialised is clearly mistaken. Access to larger numbers of molecular targets, larger numbers of drug-like compounds and faster screening technology has not led to proportionally more registered drugs (Munos, 2009; Abbott, 2010). Similarly our knowledge of the human genome has not yet paid off in full, although the large amount of genomic information now available and the falling cost of obtaining this have increased the power of molecular diagnostics and our ability to choose validated drug discovery targets (Plenge *et al.* 2013). The consequences of this have already been seen in oncology where understanding the genetic basis of survival and proliferation of particular tumour types has led to design of targeted therapies and the move toward use of these new drugs only in those patients most likely to benefit. We are thus learning more about disease processes day by day, but much of this knowledge is difficult and slow to translate into drug discovery. The regulatory environment has also become stricter with greater demands for patient safety leading to ever larger clinical trials of increased duration and cost. This has led to the industry abandoning areas of research

"We are learning more about disease processes day by day, but much of this knowledge is slow to translate into drug discovery. The regulatory environment has also become stricter."

that were seen as too difficult (CNS – see Abbott, 2010) or where prospects for return on investment were poor (antibiotics – see Coates 2012; Torjesen, 2013). The rise of governmental bodies concerned with cost effectiveness of new treatments (e.g. NICE) has also put constraints on the potential profits that can be made from new agents at a time when development costs are higher than ever before (Eichler *et al.* 2010). The medical need for new treatments has never been higher yet constraints on the drug discovery and development process are making the pharmaceutical sector less attractive as an investment.

Senior figures in the pharmaceutical industry are now saying in print that we need to reinvent the discovery process (Paul *et al.* 2010; Bennani, 2011). If we cannot close the gap between drugs losing patent protection and new product introductions then the industry will shrink. For the first time in living memory a reduction in the R&D spending of the industry has been driven by the incontrovertible fact that spending more on R&D year on year did not work (Carroll, 2010; Hirschler 2011; Piomelli *et al.* 2011). The realisation that 'doing more' was not the answer to increasing R&D productivity was slow to come. But once it was accepted that 'quality not quantity' was what was needed, then most – if not all – of the major companies proceeded to reduce the size of their internal research operations. Outsourcing, especially chemistry to India and China, and development to international CROs, closure of ex-US research institutes and increased reliance on academic collaboration were all expedients used across the industry (see McKernan, 2013). The driver now is to reduce costs where possible, get the investment right and only invest where probability of success is high (Kola & Landis 2004; Paul *et al.* 2010). Major reorganisation of R&D departments has included creation of virtual departments tasked with doing all or most research in a particular therapeutic area outside the company (e.g. CNS research at AstraZeneca – see Mullard, 2013a) and the setting up of internal business units that had to compete for funding as though they were biotechs (GlaxoSmithKline). This is coupled with a need to streamline development (FDA, 2011) and kill drugs that are not clearly an improvement over what we already have as early as feasible (Paul *et al.* 2010). It is perhaps necessary to admit the need to empower creative talent and admit that drug discovery is as much an art as a science (Douglas *et al.* 2010; Paul *et al.* 2010; Bennani, 2011). The crucial reorganisation may already be in progress with much of the creative part of drug discovery moving over to the biotech sector or to academic centres for drug discovery (Kotz, 2011; Stevens *et al.* 2011). Academic collaboration and recruitment of staff at the cutting edge of their fields facilitated by relocating research operations to academic centres of excellence is also a move being followed by most of the major companies. This phenomenon was first seen en masse in Cambridge, MA, USA, but the setting up of a substantial Pfizer research unit (Neusentis – see McKernan, 2013) and the recent decision of AstraZeneca to move their research headquarters to Cambridge, UK may herald the start of a similar consolidation of industrial research around what is seen as the academic community most likely to be supportive of innovative drug discovery. In this context it is also interesting to note that the academic contribution to drug discovery may have been underestimated in the past (Stevens *et al.* 2011). Not all academics wish to work with or in the pharmaceutical industry, but for those who do, or are prepared to give it a try, the next decade will be a time of unique opportunity (Kotz, 2011; McCall, 2013; Mullard 2013b).

Investment in new R&D facilities is being made in those countries which are seen as major future markets for drugs. It is already evident that cuts in R&D spending in the UK and US have been paralleled by an increase in spending in Asia, especially in China (Zhang, 2011). One reason for the failure of the industry to sustain its productivity has been the patent expiry of the blockbusters discovered during the 1980s so that they became generics. Subsequent new drugs have had to compete with them both on efficacy and on price. In the future it may be necessary to perform an ongoing assessment of a drug's effectiveness and safety such that the benefit–risk profile is recalibrated during the whole life cycle of the drug in question (Breckenridge *et al.* 2012). These factors are driving a shift from proprietary medicines to generics and by 2015 it is likely that generics will account for 39% of the total drug spend compared with 27% in 2010 (IMS, 2011). We are thus victims of our own success as the blockbusters of 2005 become the generics of 2015. Repurposing of drugs is now a major topic of research for industry–academic cooperation to jump-start new therapeutic approaches by shortening the development pathway (Corbett *et al.* 2012). New drugs are continuing to be discovered, many of them coming from the biotech sector (Kneller, 2010) and there is an increasing using of proteins rather than small molecule agents. Around 50% of the new drugs that will drive profitability in 2015 will be biologicals and the majority of these will be monoclonal antibodies (Nelson *et al.* 2010; IMS, 2011). Spin-out companies are arising from the large companies as a result of downsizing and these are starting to be productive, although there is still a funding gap for new companies that

can make this process difficult to initiate. There is evidence that the new model of R&D will be a triangular association of large pharmaceutical companies, small specialist companies and academic groups working very closely together. Open access initiatives where a common precompetitive objective is worked on cooperatively without intellectual property constraints are starting to take effect (Hunter & Stephens, 2010; Hunter & Wilson, 2011) and are a logical way to achieve regulatory approval for a biomarker as a surrogate endpoint for clinical trials. It has also been suggested that a systems biology approach will lead to better predictive modelling of clinical outcomes with novel approaches and that the lead in this will come from academic laboratories (see Abbott, 2008).

There is some evidence from recent observations on failure rates in clinical trials in 2011 and 2012 that we may be turning the corner and that more drugs are failing in phase II and fewer in Phase III, suggesting that the industry is now designing better trials that allow early termination of failing hypotheses (Arrowsmith & Miller, 2013). It has also been suggested that the innovation drought in the pharmaceutical industry is a myth and that current incentives do not reward true innovation, but reward companies for producing large numbers of new drugs with few clinical advantages over existing ones (Light & Lexchin, 2012). It is certainly true that incentives offered by regulatory authorities have resulted in a big increase in drugs targeting rare and orphan diseases and in both 2011 and 2012 a record number of orphan drugs were approved (Geilinger *et al.* 2013). Our world will look very different 10 years from now with an increasingly complex social, legal, scientific and political environment, but we should not lose sight of the fact that virtually all major advances in drug therapy have come from large companies and have been funded out of profits rather than philanthropy. Any remodelling of the drug discovery process needs to be in the context of a business model that allows recovery of costs and ensures that a fair reward for innovation is still achievable for those companies involved in this endeavour.

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Collaborations in industry

Collaborations between industry and academia in the context of declining productivity in drug discovery

Stuart W Hughes

Lilly Research Laboratories,
Erl Wood Manor, Windlesham

Mark O Cunningham

Institute of Neuroscience,
The Medical School, University of
Newcastle upon Tyne

It is currently no great secret that the drug discovery industry is facing major challenges. Over the last 30 years the cost of developing a new drug has been increasing rapidly, whereas the number of new agents that are approved on an annual basis has remained roughly constant. As such, the manner in which the cost per molecule is steadily rising is seen by many as unsustainable (Scannell *et al.* 2012). Alongside this situation the drug discovery industry is also being impacted by a glut of patent expiries of some its best-selling agents leading to significant decreases in revenue. Although these challenging circumstances are having a significant bearing on R&D efforts in a range of therapeutic areas, probably the greatest impact has been felt in neuroscience. It has been estimated that only around 8% of CNS agents entering clinical trials end up as successfully marketed drugs, lagged only by oncology and women's health at around 5% and 4%, respectively (Kola & Landis, 2004). As a result of this, over the last few years several large pharmaceutical companies have reduced their interest in developing new drugs for CNS ailments, with psychiatric disorders being particularly hard hit.

Given the huge and increasing expenditure on drug discovery efforts, it is important to ask why more drugs do not successfully make it through clinical trials. Twenty years ago the main reason for this was unpredictable pharmacokinetics (PK), with around 40% of molecules failing for this reason (Frank & Hargreaves, 2003). Through the use of a variety of predictive of assays this has now largely been addressed. However, what used to be a close second behind PK as the reason for failing to make it through clinical trials is now firmly established as the number one reason, namely lack of efficacy. In fact, more than half of all drugs fail because they essentially do not have the desired effect on the disease state of interest in Phase II proof-of-concept (POC) trials (Arrowsmith, 2011). Why this is the case essentially then comes down to two, not necessarily exclusive, possibilities. The first is that the exposure of unbound drug in the target organ and/or binding to the proposed molecular target were insufficient to test the therapeutic hypothesis. The second is simply that the therapeutic hypothesis was incorrect. Whilst the first of these possibilities can be addressed through the use of improved biomarkers, the second speaks more fundamentally to a lack of knowledge of human disease processes at their most basic, molecular level.

It is against this backdrop that a renewed interest in collaborations between industry and academia has emerged. Such collaborations are of course nothing new but in the last 5–10 years the nature of these, the scale on which they are occurring, and the expectations placed on them have certainly taken on a new appearance. Possibly, one of the main differences is that in earlier years such collaborations might have taken on the form of more focused, small-scale studies with a particular question in mind. For example, this might have been an academic laboratory investigating the mechanism of action of a new molecule using certain techniques and preparations that were particular areas of expertise. In contrast, it appears that collaborations now often involve multi-centred consortia focused on more fundamental and broad-reaching issues in drug discovery centred on the two possibilities for clinical failure outlined above. In many cases these collaborations comprise public–private partnerships as in the case of the EU Innovative Medicines Initiative (IMI) whereas in other instances they are supported wholly by individual companies. An example of the latter is Eli Lilly's Centre for

Cognitive Neuroscience (CCN), which is a virtual grouping of leading academics who work alongside Lilly scientists to find improved ways for developing new drugs to treat cognitive disorders. Ultimately, many of these collaborations come under the broader heading of open innovation and are based on the premise that casting the net wider and bringing more expertise and intellect to the table will accelerate the delivery of solutions to what is arguably the most significant current problem in drug discovery, that is, providing better translation between preclinical *in vitro* animal models and human disease.

Given the widespread presence of such large-scale industry–academic collaborations and consortia it is tempting to assume that bigger is indeed better and that many heads must surely be better than one or two. However, before jumping to this conclusion it is worthwhile acknowledging some of the challenges and characteristics associated with such arrangements to assess their true value to drug discovery. The first and most obvious challenge is that such collaborations are only as good as the question or questions they seek to address. Whilst this may seem a self-evident statement and one that is easy to deal with through appropriate planning, the complexity of some of the disorders being tackled in this way means that this is not the case. A case in point is the area of complex psychiatric disorders. Despite huge advances in neuroscience over the last few decades, our basic understanding of psychiatric disease at the cellular and molecular level remains scant at best. As such, understanding how to frame research to genuinely unravel the mechanistic basis of human psychiatric disease is far from straightforward. For example, developing better animal models for these most human of conditions is fraught with complications whereas using existing animal models, potentially alongside drugs previously discovered phenotypically by serendipitous means, to try and dissect the essential pathways that mediate human psychiatric disorders is equally laden with difficulties. As such, given that in such areas we know little or nothing definite about basic mechanisms, it is far from an easy to task to effectively design large collaborative research efforts that may deliver such information. Of course, one way around this is to concentrate solely on diseases where we know something very definite about their underpinnings, e.g. diseases with a known genetic cause. However, this would exclude a host of large unmet medical needs and lead to an increased focus on rare disorders which may or may not lead to more broadly applicable treatments further down the line. A second potential issue is that whilst large-scale collaborations undoubtedly open up new technical and experimental possibilities, it is important that this does not become simply a 'data binge' which may well deliver a wealth of new information about particular animal models and assay formats, but not lead to genuine new insights into human disease or robustly validated new drug targets. The key point here is that although collaborations may facilitate the conducting of many studies that would not otherwise have occurred, there is the danger that this simply constitutes 'more of the same' rather than a fundamental shift in the way that drug discovery is carried out. For example, continuing to operate on the assumption that certain disorders can be addressed by a straightforward target-based discovery effort and then simply generating additional data and assays to support that idea may be, at its core, a flawed, or at least fruitless, strategy (Swinney & Anthony, 2011). A third issue with large collaborations is their inherent organisational complexity. Ensuring that all parties work effectively in partnership to achieve the main objectives of the collaboration can be far from straightforward, meaning that it is easy for the scientific endeavour to become fragmented and lack cohesion. These challenges aside, it is our view that the coming together of academia and industry in large numbers to try to solve some of the most pressing medical needs of the 21st century provides a unique opportunity to further science in a way that may not be possible by other means. As long as such collaborations are directed at the right goals, are aimed at tackling well-defined problems related to human disease, and provide genuine novelty and unity in the way they try to achieve these ends, they would appear to offer a powerful route to innovation.

Despite the emergence of large consortia-based collaborations, the importance of more small-scale traditional collaborations should not be overlooked or discarded. Indeed, such collaborations can have immense value in addressing very specific scientific issues. In terms of a successful outcome, a key characteristic of these collaborations is the coming together of different parties with a clearly shared goal to solve a particular problem. In contrast, the practice of pharmaceutical companies funding PhD students and postdocs in academic laboratories with few questions asked and minimal expectations imposed should be considered a thing of the past. A positive example of a successful small-scale collaboration is one that recently took place between one of the authors (S W Hughes) and Richard Horner at the University of Toronto. These two parties came together with the aim of understanding the cellular mechanisms that cause the loss of muscle tone (i.e. atonia) in the tongue musculature during rapid eye movement (REM) sleep, a process inextricably linked with the sleep-disordered breathing condition, obstructive sleep apnoea (OSA). Through the use of a unique *in vivo* rodent assay developed in Horner's lab, which allows the monitoring of genioglossus muscle tone during natural sleep and wake states whilst providing the capacity to introduce pharmacological agents directly to the corresponding motor neuron pool, i.e. the hypoglossal motor nucleus, this led to the development of a new framework for explaining REM sleep atonia based on the opening of a certain class of K^+ channels in this sleep state and thereby challenged the dogmatic view that this phenomenon depends on glycinergic inhibition (Grace *et al.* 2013).

In summary, it is evident that collaborations between academia and industry have taken on a new form in recent years. This has largely been driven by the declining productivity and increasing costs associated with delivering new drugs to the market, which in turn is the result of a high failure rate in Phase II clinical POC studies. As such, large scale consortia have emerged with the main goal of improving translatability between preclinical models and human disease states. Whilst this is undoubtedly a positive development, it is clear that certain challenges exist with such arrangements which should be considered carefully in order to maximise their output in terms of providing definitive new insights into human disease and potential routes to treating them. Alongside these larger efforts, the undoubted value of smaller, traditional collaborations should not be underestimated. Indeed, the manner in which such collaborations naturally facilitate the focused investigation of very specific problems allied to the practical ease and efficiency with which they can operate means that although they may not provide the impressive bandwidth of large consortia they may ultimately offer the best value for money.

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Across the great divide

Academicians and industrial scientists often regard each other with suspicion. But with some understanding, physiologists can move between the two spheres, according to *PN* Editor Mike Collis, whose own career has bridged the divide.

Michael Collis

Editor, *Physiology News*

"There are exceptional scientists working in both spheres of research. They have different motivators – in academia the question and subsequent publications, in industry the project and a useful product."

There is a lot of interest from funding groups these days in 'intersectorial mobility'. Moving between academic and industrial research environments is seen as a positive step to increase the breadth of a scientist's experience and facilitate the exploitation of his or her discoveries. There are of course important differences between the two sectors and attempts to apply a 'one size fits all' approach to a scientific career would be a major error. We need blue-sky academic research to make the big discoveries that come unexpectedly 'from left field' and we also need the industrial scientist to translate those discoveries into practice. But are the environments that these two groups work in so different that one cannot move between them successfully?

Many academic scientists regard industry with suspicion laced with a fair number of misconceptions. A move from academic research (where we all start by doing a research degree) to industry is often regarded as an undesirable last resort. "Well if this grant isn't funded then I could always go and work in industry" is a sentiment I have often heard expressed. This isn't the case and if you are not successful in an academic science career then you are unlikely to cut the mustard in industry either. Industry (like academia) wants to recruit the best scientists and a lacklustre academic career will not impress. In both environments you need to make a strong enough case to get someone to support your research, in academia a funding body, in industry a research director or management team. Convincing people to fund your research is a skill that scientists need in both environments. Other misconceptions about working in industry include "You get told what to do". Well that may be the case if you are a junior technician, but if you hope to make it as an industrial scientist, it's you who will need to convince your research director of what you should be working on. If your project isn't delivering, then you should be the one addressing the issues and even proposing closing it down, if the obstacles are insurmountable. In industry, as in academia, failure isn't closing a no-hope project, failure is keeping it going too long. There are, however, unfortunate times in industry when major strategic changes in a company research portfolio are imposed from above and you do get told to work in a different area. This is disruptive and can be demotivating for those who find that their research project has been transferred elsewhere without them. In my experience, good scientists have no problem in transferring skills from one project area to another and often bring new insights because of their different background. "You can't publish your work in industry" is a further misconception. In industry you are working towards a product that needs to be protected by a patent and this may delay publication of your work in the public domain. You may have to wait, but you can still publish. This type of time constraint can also apply in academic research, where there is a potentially valuable product or concept that you or your institution need to retain ownership of.

A positive facet of an industrial career in the past was better job security for scientists than in academia. Unfortunately this is no longer the case and a career in industry is as insecure as it is in academic research.

Misconception is not of course just one sided. Industrial scientists often regard academics as driven by ego, not used to meeting deadlines and vastly overvaluing the importance of their discoveries. In industry everything is measured and reward and progression are usually based on performance against agreed

quantitative goals. Although there are attempts to measure academic performance (usually based on publications) the assessment of performance in academic circles is much less clearly defined and based on acceptance and acknowledgement by peers. Industrial scientists often think that academic project or strategy meetings are too long and involve much discussion but few decisions. Industry likes bullet points and quick decisions, academics like discussion. Do academic scientists have stronger individualist tendencies and find it harder to work in multi-disciplinary teams? Some industrial scientists would say yes to this question. But with the increasing trend to a research group approach in many universities, this is becoming less true.

In my own experience there are exceptional scientists working in both spheres of research, but they have different motivators. In academia the major motivation is publication and although the potential 'impact' of academic research figures high on funding council agendas, success in an academic career is still highly dependent on the quality and quantity of publications. The industrial scientist is motivated by the desire for a product from their research that can have a direct or indirect benefit to man. It is the project not the question that is king. This is not to say that academic researchers are not motivated by the application of their research, but it is rarely the primary driver.

Intersectorial mobility does not necessarily mean burning your boats and changing your career path permanently. Early in a career you can experience both academic and industrial research before committing to either by enrolling for a Collaborative Awards in Science and Engineering (CASE) PhD studentship. These are offered by both the MRC and the BBSRC and provide an excellent training in both research environments. The student benefits from having both an academic and an industrial supervisor and performs part of his or her research project (at least six months) at the industrial laboratory. This is an ideal way to get a taste of the way research is conducted in both academia and industry and is often a stepping stone to further academic–industrial collaborations and interactions for both supervisors and students.

For more established academic researchers, the research councils offer a number of fellowships and grants to facilitate collaboration and exchange between the two sectors such as Industrial Partnership Awards, Flexible Interchange Programmes from the BBSRC, and 'MICA' awards for collaboration and secondment with industry from the MRC.

But what about a permanent move from one sector to the other? This is more challenging than a short-term secondment or collaborative project. Some people are just better suited to one environment than the other and a permanent move would not suit them. However, moving from academia to a job in industry is certainly possible at most stages in an academic career. But as is the case with most change, it's easier to do when you are young and haven't become steeped in the ways that one sector operates. A stellar academic research track record in an area of interest to the industrial concern will certainly be a strong factor supporting recruitment. It is probably harder to move from industry into academia once you have become established in the former because the current system of assessment in academia depends so much on publications and successful grant applications – which may be less for the industrial scientist. (It is a pity that academic research assessment systems do not value patent applications and collaborative research more highly as this would encourage intersectorial activities and mobility.) However, these hurdles are by no means insurmountable and I have a number of colleagues who have successfully moved from industry to academia, either because they preferred the latter or because their industry employer moved their jobs to a different country. In Scandinavia, leading scientists often have joint appointments between a university and an industrial concern. This model seems to have worked well when one considers the medical innovations introduced by the Swedish pharmaceutical industry, but it is not a model that has been taken up in the UK to my knowledge. Serving two masters can be a tricky business.

My experience of moving between sectors has been a positive one; I have learnt from both and I would encourage others to do the same. This sort of mobility could be encouraged by industry helping academics to better understand their drivers, success rates and time scales, by having regular meetings with key academic groups and by organising visits to each other's sites. An informed and pro-active academic liaison officer in industry can also help to put academic scientists in touch with counterparts in the company who have similar research interests as a starting point for collaboration and exchange. Academic institutions can help the process by pro-actively seeking collaborations and exchange opportunities, by facilitating contract discussions and, most importantly, by recognising that a significant industrial collaboration or a secondment to industry should be valued just as much as highly cited research papers when it comes to discussions of reward and promotion.

Q&A: Placements in industry

Industry and academia can seem like two different worlds. Coming from academic study, how can an early-career physiologist know whether the commercial concerns of industry will constrain their curiosity, or the fantastic funds and facilities feel like freedom? *PN* talks to two students of physiology – at different stages in their studies – who have sought first-hand experience of both environments.

Rebecca Wadey

Cardiff University & AstraZeneca

What are you studying and what led you to this?

I am currently studying for my PhD entitled 'Validation of Translational Biomarkers of Renal Injury' at Cardiff University. It's a four-year, BBSRC funded Industrial CASE studentship with AstraZeneca. Prior to starting my PhD, I did a Biomedical Sciences BSc degree at King's College London. My first exposure to working in a lab was during my third year placement with Cathy Shanahan studying vascular calcification. I really enjoyed my placement in her lab and decided to do a research based masters after I graduated - that's what brought me to Cardiff! I worked in Sarah Hall's lab for the year studying the control of cardiac myocyte cell volume and then got my PhD studentship in Daniela Riccardi's lab just down the corridor!

How did you come to do a placement at AstraZeneca?

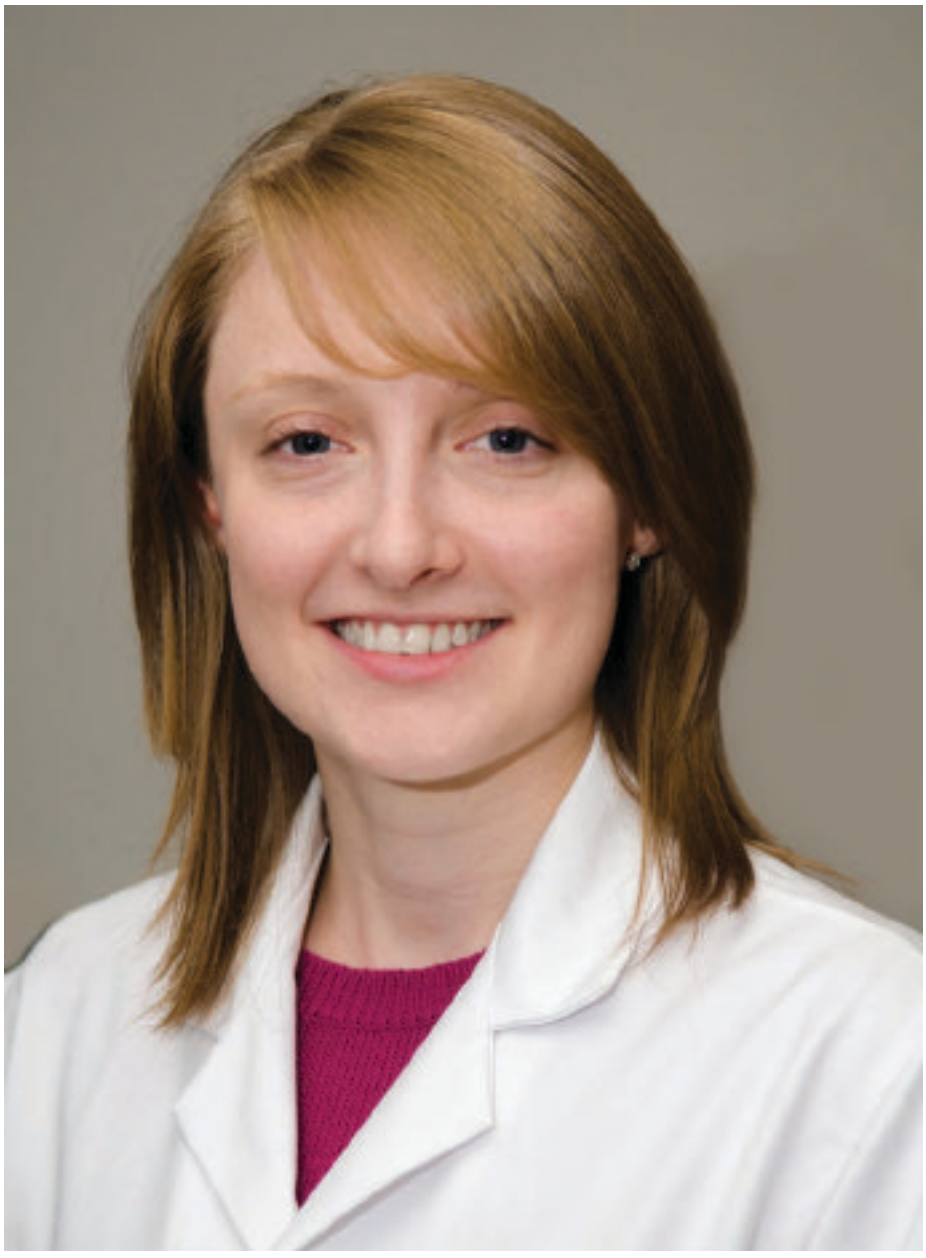
Students with the Industrial CASE studentship have to spend a minimum of three months on placement with the industrial partner, and in my case this was AstraZeneca. AstraZeneca is a multinational biopharmaceutical company with a large research and development site in Cheshire, and I moved there for the duration of my placement. Although my placement was a requirement for completion of my PhD, I went there as they had access to equipment and samples that were not available to me in Cardiff.

What are you doing there?

My PhD centres on the validation of novel biomarkers of drug-induced acute kidney injury. Currently, a diagnosis of acute kidney injury is made by either histopathological examination, which requires an invasive biopsy in humans and which is a terminal procedure in preclinical species, or by monitoring changes in serum creatinine and blood urea nitrogen, parameters which change when kidney function declines. The problem with serum creatinine and blood urea nitrogen is that they are very insensitive and non-specific and therefore an extremely large amount of kidney injury has to occur before changes are seen.

I went to AstraZeneca to help validate some of the novel biomarkers of kidney injury that have recently been identified. Ideal biomarkers should identify injury early, localise the site of injury, reflect the degree of injury and be present in urine so that they can be tested for using a dipstick. In addition, ideal biomarkers should be applicable to both preclinical species and humans. I carried out immunohistochemistry for six biomarkers on kidney tissue obtained from rats which had been treated with Cisplatin, an anti-cancer drug with a known nephrotoxic side effect, and correlated tissue expression with urinary presence, and the work that I did on my placement has recently been published! [Wadey RM, Pinches MG, Jones HB, Riccardi D, Price SA (2013). Tissue expression and correlation of a panel of urinary biomarkers following Cisplatin-induced kidney injury. *Toxicologic Pathology*].

Instead of using whole animals to screen drugs for nephrotoxicity, AstraZeneca could potentially expose cultured renal cells to drug candidates and test for biomarker changes. This would enable them to screen large numbers of potentially therapeutic drugs for nephrotoxic side effects more



"The atmosphere was very different to working within academia where timelines can be more flexible and projects can go down a number of different avenues."

quickly and in a more cost-effective way. This also complies with the ethical framework of animal experimentation, the 3Rs – reduce, replace, refine – and is what I am currently working on back in Cardiff.

What was your experience in industry like?

My placement at AstraZeneca gave me an invaluable insight into how biopharmaceutical companies work. I was able to use really high-tech facilities, ranging from the equipment I used to carry out immunohistochemistry to the computer analysis software I used to quantify the biomarker changes. In addition, I was able to work with people who are specialists in drug safety assessment and got to see first-hand how drugs progress though preclinical development. The people working at AstraZeneca were very goal-orientated. They have to meet targets and get results quickly in order to progress promising projects and ultimately make money for the company. The atmosphere was very different to working within academia where timelines can be more flexible and projects can go down a number of different avenues.

Has your experience at AstraZeneca changed your future plans or expectations?

My placement at AstraZeneca has definitely made me consider a career in industry. Just like my PhD, I'd quite like to get a job where there is a strong collaboration between an academic group and an industrial partner as I think you then get the best of both worlds!

Devon Shannon

Exeter University & GlaxoSmithKline

What are you studying and what led you to this?

I'm at Exeter University at the moment, studying molecular biology [Bachelor's degree]. I've already done two years and next year will be my final year. I've not always been into science. At GCSE level I wanted to go into art and media studies and be an interior designer. It was one of my teachers who said to me, 'You're wasting your talents in science if you go and do art and media studies'. So it was a complete change in career trajectory. One of the things that made me think, yes, I do want to do science as a degree was that I was put into a team of three people for the Royal Society of Chemistry's Schools' Analyst competition. Quite geeky, but very fun! It involved A-level students from across the UK competing to see who had the best skills in the lab. That was the first time I'd had any experience in a university laboratory and got my hands on equipment that we weren't allowed to touch in sixth form!

How did you come to do a placement at GlaxoSmithKline (GSK)?

The course that I applied for at Exeter, molecular biology, was offered as either a three-year course or a four-year sandwich course. My tutors at A-level all said 'Do the four year course. We know it's an extra year and that might seem like a lot of effort, but it will be well worth it and' – the classic phrase – 'it will look good on your CV'.

We didn't get a lot of guidance on finding a placement from uni', it was more a case of independent research to find the job advertisements. I knew it would be a challenge and incredibly competitive, but I wanted to go for a 'big pharma' company, because I thought I was more likely to get a diverse range of experiences there than if I went to a small or more specialist company. It was a case of spending ages trawling through websites looking at different company sites and the advertisements they had on their careers pages. I think it was something like 100 applications for every one position. So it was incredibly competitive. One thing that I think really helped me was that the careers advisers at Exeter are absolutely fantastic! There's a whole building dedicated to careers and they help you with CVs, applications, what to do in interviews and assessment centres and they give you loads of advice. You can show them your CV and have a mock interview to prepare for the real thing. So I managed to prepare quite well and I felt almost like I'd done it before, so that when I was sitting there in the interview – and I sat in three for placements at GSK – I felt quite comfortable, like I knew what I had to do. One interview was with their respiratory department, one was with immuno-inflammation, and one with their pre-clinical imaging team, which is where I actually got the job.

What are you doing there?

My job title is *In Vivo* Imaging Scientist. What we're aiming to do is to use MRI and µCT to look at diseases and how they progress in live animals. Basically I've been working out how to study fibrosis. Fibrosis is a progressive disease that takes years and years to develop, so, as you can imagine, if you're trying to study it in humans then you're going to be there a long time waiting for the chronic stages. Similarly in animals, once you've induced the disease, it takes a long time to develop, so you have to wait quite a while before you can measure it and work out if any drugs you've used have actually worked. So what I'm looking at doing is developing a new mouse model which should hopefully give you a read-out of where the fibrosis is developing within a few days to a few weeks. That will significantly shorten animal studies and then you'd be able to say yes or no, this drug looks like it is or isn't working much earlier on. This is great for lead optimisation, so you can progress effective drugs to clinical trial much quicker.

One of the reasons why I applied for this job is because *in vivo* is something we don't get the opportunity to do at uni'.

What was your experience in industry like?

Going into an industrial lab is a completely different world from university. There are things at university that you think of as being very advanced because you've never used them before, such as Gilson pipettes and centrifuges, until you go into GSK and suddenly you're confronted with equipment you've never seen before! What you learn in university is transferable and you'll be able to use the basic lab skills you've learnt, but there is much more high-tech equipment in the lab, combined with more complex processes. It really is a steep learning curve.

"One of the reasons why I applied for this job is because *in vivo* is something we don't get the opportunity to do at uni'."

The atmosphere in the lab is very much the same as in the university lab, where you're all chatting about work but it's a mutual interest, so sometimes it doesn't feel like you're working. It is a very friendly atmosphere.

All animal studies were ethically reviewed and carried out in accordance with Animals (Scientific Procedures) Act 1986 and the GSK Policy on the Care, Welfare and Treatment of Animals.

Has your experience at GlaxoSmithKline changed your future plans or expectations?

It's not changed my plans, but it has confirmed that this is what I want to do. I think it's probably increased my confidence that I can do this. Now, instead of thinking 'Oh, God, that's going to be loads of education and loads of exams to get there', I'm thinking, actually, I'd really, really like to work towards that.

Bone loss in microgravity

That bone is lost in space is now commonly known, but this recognition was quite a surprise when human spaceflight began. What is less well known, but no less true, is that the loss concentrates on the leg bones. Is it caused by fluid shifts, simple mechanics or space food?

Jörn Rittweger

German Aerospace Center, Cologne, Germany and Manchester Metropolitan University, UK

Petra Frings-Meuthen

German Aerospace Center, Cologne, Germany

Loss of density in the leg bones can amount to a reduction of one-quarter within 6 months of spaceflight (Vico *et al.* 2000), a magnitude and rate that seem to outweigh the bone losses of 5–10% experienced by women after menopause. A substantial risk of fracture would thus arise for long-term missions were they done without adequate countermeasures. So, how could we try to prevent that kind of bone loss, or, as the physiologist would say, what is the cause of it?

Fluid re-distribution in space

Astronauts, when afloat in space, define 'up' as where their head is. Fluid cannot take such arbitrary decisions, but has to move as pressure dictates. An important source of venous blood pressure arises from the tension of the vessel walls. This tension is greatest in the lower legs, thus improving the return of blood when we are upright. When we are not, including sojourns in microgravity, a good half litre of blood is pushed towards the head, and this drainage is thought to cause the notorious stork legs and the 'puffy' face in space. A clever school of thought had counted together the fluid redistribution and leg-accentuated bone loss in space and proposed that perfusion pressure gradients drive bone alterations. As highlighted in Charles Turner's beautiful polemic (Turner, 1999), there even seems to be a small gain in bone mineral content (BMC) in the skull (see Fig. 2a), thus yielding a perfect match between hydrostatic pressure change and bone loss for (some of) the data gathered during a bed rest study by Adrian LeBlanc's group (LeBlanc *et al.* 1990) with dual energy x-ray absorptiometry (DXA).

More recent evidence, however, contradicts this hypothesis. We have to remind ourselves that DXA only assesses the two-dimensional projection of bone mineral and soft tissues. As such, it is unable to provide a three-dimensional description. Moreover, its outcome is likely to be affected by fluid shifts, depending on the software used. A more modern approach with computed tomography demonstrates, for example, that immobilization-induced bone loss is greater at the proximal end (close to the knee, i.e. upper) than in the shaft of the human tibia (see Fig. 2b). This is found in bed rest (Rittweger *et al.* 2005, 2009) as well as in paraplegia (Rittweger *et al.* 2010), and it should not happen if bone losses were solely determined by fluid pressure changes. As to paraplegia, it is also noteworthy that passive standing of patients does not prevent bone losses (Goemaere *et al.* 1994), which again should not be the case were the postulated fluid pressure mechanism effective. Finally, tibial bone is also lost in unilateral lower limb suspension (ULLS), as demonstrated in Fig. 2c (Rittweger *et al.* 2006), which banefully erodes that postulated hypothesis. So, we probably need to employ another school of thought.

Figure 1. ESA astronaut André Kuipers when docking at the International Space Station (ISS). The cephalad fluid shifts, as well as the musculoskeletal effects of microgravity can be replicated on Earth by bed rest with –6 degrees head-down tilt. More recently, unilateral lower limb suspension has been established as a more localized model of disuse.

Mechanics – from single cell effects to musculoskeletal interaction

There is now ample evidence that bones adapt to mechanical stimuli (Rubin & Lanyon, 1987), although how exactly this mechano-adaptation works is unknown. Osteocytes, i.e. cells that reside within the solid phase of bone tissue, are thought to play a crucial role in it, and communication between them and osteoblasts and osteoclasts involves a symphony of paracrine signals such as RANKL, osteoprotegerin, sclerostin, DKK1 and others. Bone loss in terrestrial immobilization and in space could thus be regarded as a mechano-adaptation of bone that removes unnecessary material. This notion receives support by the way in which bone losses recover after bed rest; the accrual rate is remarkably high, and at the same time extremely accurate in anatomical terms (Rittweger & Felsenberg, 2009).

But where do the mechanical stimuli that matter to bone come from? It is true that many cells, including bone cells, are directly responsive to gravity. However, the forces caused by gravity *per se* are very small, e.g. 0.1 pN for an osteocyte in its aqueous environment (Cowin, 1998). As already stated, bone losses occur in the legs, but not in the arms, both in bed rest, where gravity is at work, and in space, i.e. in microgravity. It is tempting to conclude that bone losses are somehow related to the supporting function of the legs. However, as already stated, passive standing is quite ineffective for bone in paraplegic patients. On the other hand, functional electrical stimulation of paraplegic muscles can increase BMC in the local bones (Belanger *et al.* 2000). Is it possible that muscle contractions play a decisive role then? Mechanical engineering usually focuses on the largest loads expected for a structure. And indeed our muscles all work against short levers, and are therefore expected to generate the largest forces in the bones, not only in the arm but also in the leg (Maganaris *et al.* 2011). In line with this 'muscle–bone' hypothesis, resistive exercise during bed rest fails to maintain bone when ineffective for muscle (Rittweger *et al.* 2005), but proves an effective countermeasure when it does preserve muscle strength (Shackelford *et al.* 2004; Rittweger *et al.* 2010). Finally, direct evidence from a recent study of the DLR lab in Cologne demonstrates that gravitational loading of the tibia per se is insufficient to

Microgravity on board the ISS

Astronauts on board the international space station fly in a low-Earth orbit, at a height of approximately 400 km. Although Earth's gravity is almost completely effective at this distance, the station's velocity of 7 km per second causes a centrifugal acceleration of an exactly equal force, cancelling-out the Earth's pull. As a result, astronauts are afloat onboard the station, and the so-called 'microgravity' is only disturbed by minor imperfections of the orbit, e.g. by aerodynamic drag.

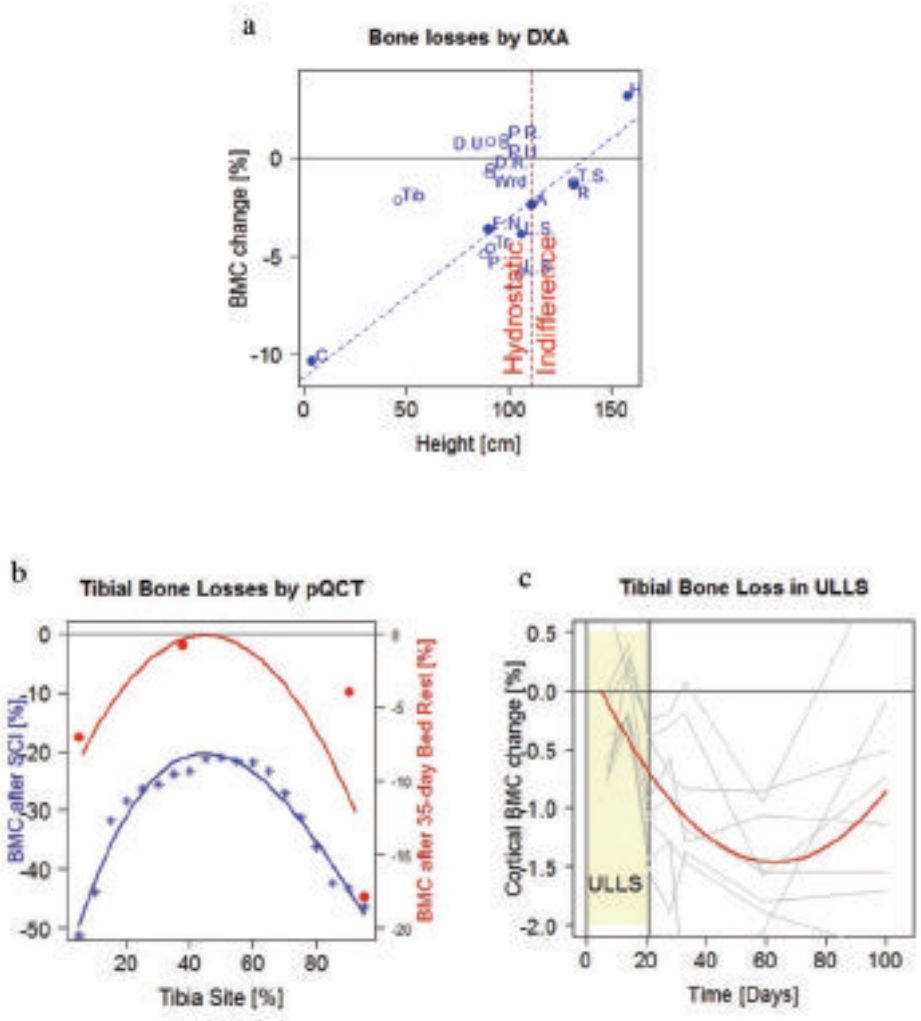


Figure 2. Some of the evidence for and against the 'fluid pressure' hypothesis. a, changes in bone mineral following 17 weeks of strict bed rest as assessed by dual energy absorptiometry (DXA). The original data (LeBlanc *et al.* 1990) from each anatomical region are plotted against the relative height within the body (Clauser *et al.* 1969). A strong correlation exists for the data included in Turner's perspective note (Turner, 1999), but not for the rest of the original data (LeBlanc *et al.* 1990). Moreover, even for the restricted data set, the regression predicts bone losses for the hydrostatic indifference level, which speaks against hydrostatic fluid pressure as the sole mechanism. C, calcaneus; F.N., femoral neck; R, ribs; H, head. b, bone losses at different levels within the tibia as assessed by peripheral quantitative computed tomography (pQCT). This technique allows 3-dimensional assessments. The 0% and 100% sites correspond to the lower and upper tibia ends, respectively. Bone losses are substantially greater at both ends than in the shaft, both after 35-day bed rest (Rittweger *et al.* 2009) (red) and in paraplegic patients (Rittweger *et al.* 2010) (blue). Curves illustrate 3rd order polynomial fits. Again, these observations undermine the concept of hydrostatically driven mechano-adaptation. c, changes in distal tibia BMC as assessed during, and in particular following 24 days of unilateral limb suspension (Rittweger *et al.* 2006). Grey curves denote time courses of individual subjects, and the red curve displays a 2nd order polynomial fit.

maintain bone mass, further establishing the specific importance of muscle contractions for bone (Ducos *et al.*, in preparation). Thus, there is sufficient evidence now to put muscle–bone interaction in the first line of rationales for countermeasure development – but will this be all that there is to the story, physiologically speaking?

Hormonal alterations and diet

We all know that diet matters to our bones. At least we seem to know this for calcium and vitamin D, which are probably the two mostly investigated agents in our daily diet. Of note, some people had initially thought that bone loss in space is caused by vitamin D deficiency. This proposition has now been abandoned, and dietary recommendations for astronauts are no higher than those for the terrestrial population. But what about the plethora of other nutrients that affect bone metabolism either positively (e.g. vitamin K, potassium, alkaline forming food) or negatively (e.g. high NaCl intake, acid forming food) – could any of those contribute?

As it happens, people seem to lose some sense of taste whilst in space. Due to food conservation and to compensate for the loss of flavour, astronaut's food items are often very salty. This could be cataclysmic, because high salt intake is likely to foster calcium excretion and bone resorption, through an acidotic shift in the *milieu intérieur* (Frings-Meuthen *et al.* 2008). Even more importantly, high salt intake can double bed rest-induced bone resorption (see Fig. 3) (Frings-Meuthen *et al.* 2011), and the same has been found for nitrogen losses, indicative of either impeded protein synthesis or increased degradation rate in the musculature. These detrimental effects of salt on nitrogen balance can be neutralized by a more alkaline diet (Buehlmeier *et al.* 2012), so that space cuisine has nowadays become an important playground for countermeasure development – and thus for physiological research!

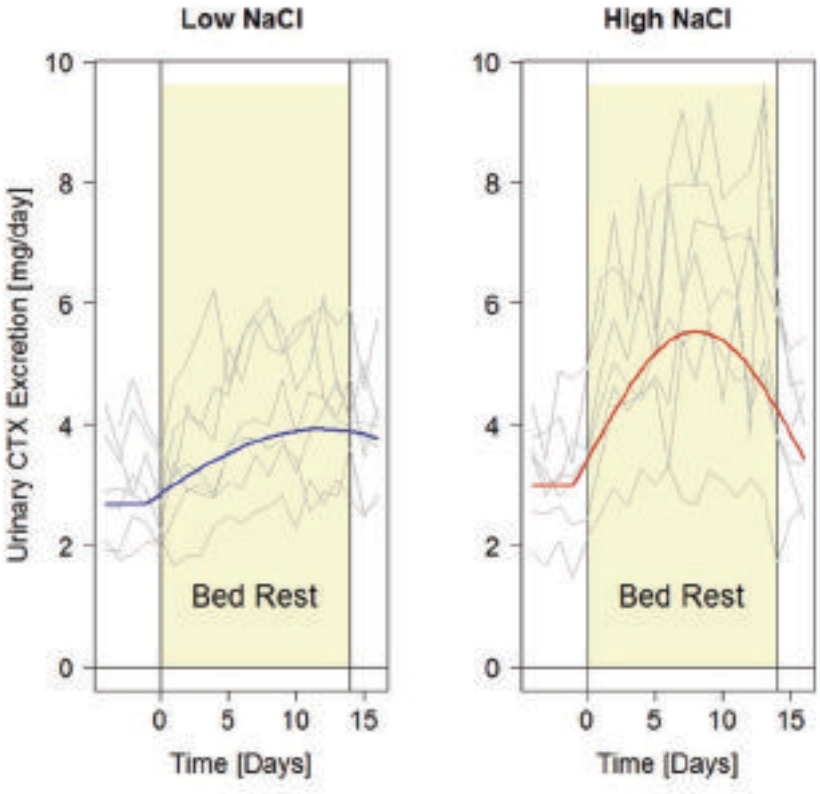


Figure 3. High salt diet boosts bed rest-induced bone resorption. In a cross-over designed 14-day bed rest study, subjects once received a diet low in NaCl (0.7 meq Na^+ kg^{-1} day^{-1}, left diagram), and once a diet that was high in NaCl (7.7 meq Na^+ kg^{-1} day^{-1}, right diagram). In both diagrams, urinary excretion of the c-terminal telopeptide (CTX) is plotted over time, and the effect of bed rest is doubled with the high salt diet. Similar effects were observed for nitrogen balance.

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Statins and implications for fetal brain sparing during hypoxia

Our time in the womb is not straightforward. As a growing fetus, our dividing cells require appropriate amounts of nutrients and oxygen. Limitations in this supply may lead to rapid deterioration in fetal wellbeing, which can be fatal or trigger serious, long-lasting consequences. Do statins help or harm the hypoxic fetus?

Andrew Kane, Emilio Herrera, Avnesh Thakor & Dino Giussani

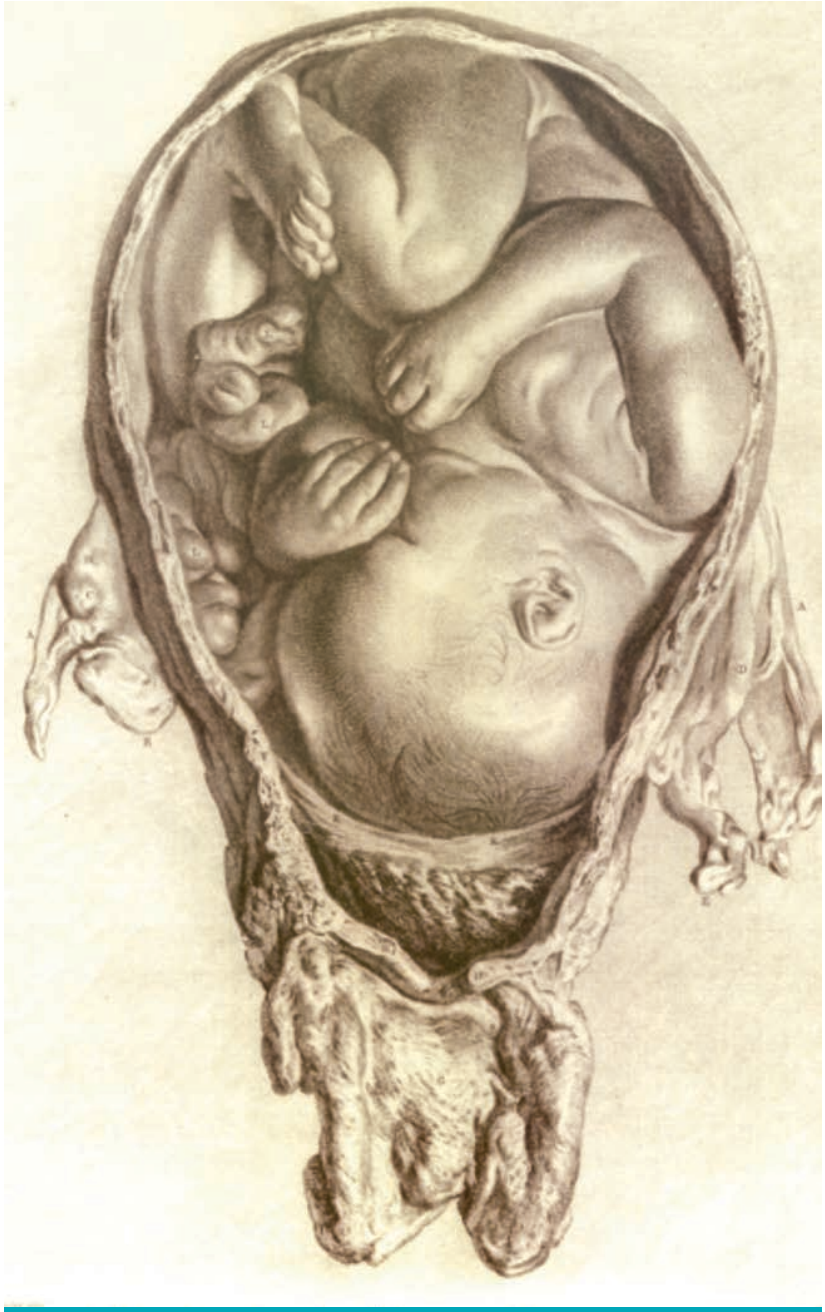
University of Cambridge, UK

Sadly, despite advances in clinical obstetric practice, the occurrence of reductions in fetal oxygenation or hypoxia represents a common, serious challenge with significant chances of long term morbidity (e.g. hypoxic–ischaemic encephalopathy and cerebral palsy) or mortality for the neonate affected (Low, 2004). Fetal hypoxia in adverse pregnancy may arise during pre-eclampsia, placental insufficiency, placental abruption or umbilical cord occlusion. Fetal hypoxia may also occur, secondary to the composition of the maternal environment (e.g. high altitude, polluted air, smoke and carbon monoxide), maternal cardio-respiratory disease or as a result of maternal anaemia.

The strategy of an individual to withstand episodes of hypoxia differs in fetal and postnatal life. In the simplest terms, in the postnatal period, our physiological response to acute hypoxia is to increase our alveolar ventilation rate and cardiac output and decrease our peripheral vascular resistance, in an attempt to maintain blood oxygen delivery to our respiring tissues. However, the fetus has no such ability to increase pulmonary oxygenation and has to survive with any reduction in oxygen delivery imposed by the placenta or the maternal environment. Using the late gestation sheep fetus as the animal model of choice, it has been shown that the fetal strategy is to make best use of the available oxygen supply, redistributing cardiac output away from the peripheral organs, such as the gut and limbs, and towards more essential circulations, such as those perfusing the fetal brain (Cohn *et al.* 1974). This 'brain sparing' defence to acute hypoxia during fetal life is achieved through coordinated neural, endocrine and metabolic mechanisms. We know that the fetus can sense hypoxia via the carotid body chemoreceptors, and that this information is relayed to the fetal brain via the glossopharyngeal nerves (Giussani *et al.* 1993). In turn, there is activation of both the sympathetic and parasympathetic arms of the autonomic nervous system. The neural component of the sympathetic nervous system drives vasoconstriction of the peripheral circulation, hence increasing peripheral vascular resistance and reducing peripheral blood flow. In contrast, cerebral vascular resistance is decreased, directing a greater proportion of blood flow to the fetal brain (Rudolph, 1984; Giussani *et al.* 1993). If the period of hypoxia is prolonged and/or severe, the fetus will release a vast array of agents into the fetal circulation, including catecholamines, cortisol, angiotensin II, vasopressin and neuropeptide Y, which maintain peripheral vasoconstriction and, thereby, the redistribution of blood flow (Giussani *et al.* 1994). In addition, the fetus mounts a metabolic response. Hypoxia results in an increase in anaerobic respiration with less ATP generated per unit glucose. Therefore, elevations in fetal plasma catecholamine levels drive a hyperglycaemic

response resulting from a decrease in glucose uptake and utilisation by peripheral tissues and an increase in hepatic glucose production by promoting glycogenolysis and gluconeogenesis (Jones, 1977; Jones *et al.* 1983). The fetal lactic acidaemia arises from anaerobic metabolism of glucose in hypoxic fetal tissues, particularly in the hind limbs where blood flow and oxygen delivery markedly decline (Boyle *et al.* 1990). Interestingly, many aspects of this fetal defence to hypoxia are well conserved across species, from reptiles to birds and mammals, including non-human primates and the human fetus (Giussani, 2006).

Recently, work in our laboratory has focused on the contribution of the fetal vasculature itself to the fetal redistribution of blood flow during acute hypoxia. In addition to neuroendocrine control, it is now recognised that the cellular oxidant milieu is an important modulator of vascular resistance (Chen & Keaney, 2004; Valko *et al.* 2007). In the adult vasculature it is established that there are increases in the production of the superoxide anion ($\cdot O_2^-$), which will react with nitric oxide (NO), reducing its bioavailability. An increase in the vascular ratio of $\cdot O_2^-$:NO will thus promote vasoconstriction, and the reverse will favour vasodilatation. Reactive oxygen species (ROS) are generated through pro-oxidant systems including the mitochondrial electron transport chain, uncoupled eNOS, xanthine oxidase, NADPH oxidase and cytochrome P450. Under normal physiological conditions, ROS are continuously degraded by antioxidant defences including enzymatic disposal by superoxide dismutase, catalase and glutathione peroxidase, and/or by free-radical scavenging molecules such as vitamins C and E, melatonin and the carotenes (Valko *et al.* 2007). However, at higher concentrations, $\cdot O_2^-$ may react with NO instead of being degraded or binding to an antioxidant molecule, thereby having implications for cardiovascular regulation. In the fetal circulation, it has been appreciated for some time that NO contributes to the maintenance of blood flow in many vascular beds, including the umbilical, cerebral, myocardial, femoral and carotid circulations, as inhibition of NO synthesis leads to pronounced increases in vascular resistance. It is also known that during acute hypoxia, enhanced NO opposes chemoreflex and endocrine vasoconstrictor influences in the femoral vascular bed, thereby fine-tuning the fetal peripheral vasoconstrictor response to hypoxia (Morrison *et al.* 2003). However, the role of free radicals and their interaction with NO in the control of the fetal circulation in health or disease had not been established until very recently.



Near-term human fetus in utero with placenta previa. This is plate XII of William Hunter's *Anatamio uteri humani tabulis illustrata*, The Anatomy of the Human Gravid Uterus Exhibited in Figures. Birmingham, John Baskerville, 1774.

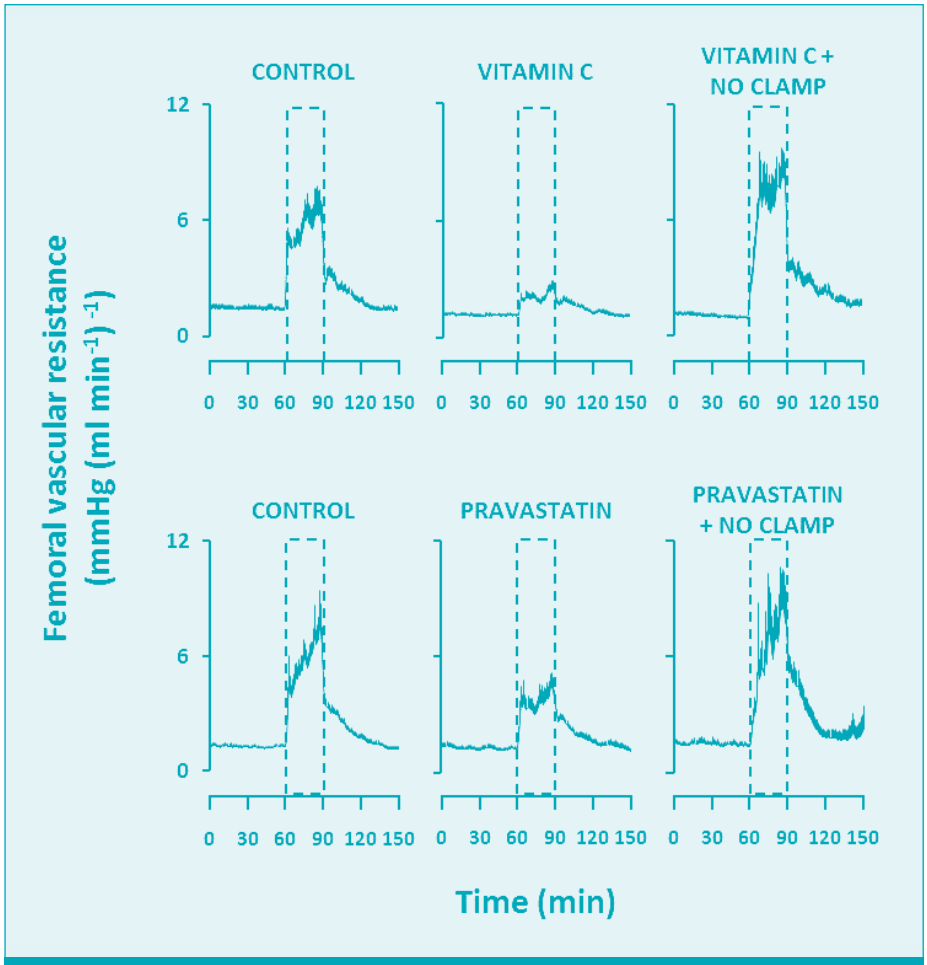


Figure 1. Femoral vascular resistance during 1 h of normoxia, 0.5 h of hypoxia (dashed box) and 1 h of recovery for late gestation fetal sheep during saline infusion (n = 6/7), treatment with vitamin C or with pravastatin (n = 6/7) or treatment with vitamin C or with pravastatin during the NO clamp (n = 6/7). Values represent the mean ± SEM calculated every minute. Experiments with vitamin C or with pravastatin are from different studies. Modified from Thakor *et al.* (2010b) and Kane *et al.* (2012).

Work in our laboratory has now shown that treatment of fetal sheep with the antioxidants vitamin C or melatonin, which are able to quench O_2^- in the circulation, promotes significant vasodilatation in the umbilical vascular bed, leading to significant increases in umbilical blood flow (Thakor *et al.* 2010a). In another study published in *The Journal of Physiology*, fetal treatment with vitamin C led to dilatation of the fetal femoral vasculature during basal conditions and impaired the fetal femoral constrictor response to acute hypoxia (Fig. 1; Thakor *et al.* 2010b). The data suggest that antioxidant sequestration of $\cdot O_2^-$ within the fetal vasculature, and prevention of the reaction with NO, increase the bioavailability of NO, promoting vasodilatation and, thereby, increasing flow under basal conditions and opposing peripheral vasoconstrictor influences during stimulated conditions, such as during fetal hypoxia. This was later confirmed as fetal treatment with antioxidants in the presence of the NO clamp, an *in vivo* technique that blocks NO synthesis without affecting basal cardiovascular function (Gardner & Giussani, 2003), restored the magnitude of fetal peripheral vasoconstriction (Fig. 1).

The discoveries of the operation of an oxidant tone in the fetal vasculature and its manipulation with antioxidants driving changes in blood flow have important implications for the use of drugs in pregnancy that increase NO bioavailability. One such example is HMG-CoA reductase inhibitors. Statins inhibit the rate-limiting step in cholesterol synthesis and have therefore become some of the most effective and widely prescribed drugs for the primary and secondary prevention of coronary heart disease (Steinberg, 2008). In addition to their lipid lowering action, additional beneficial effects on the circulation have been noted, including decreases in arterial stiffness, reductions in platelet aggregation and improvements in vascular endothelial function. These benefits have been credited to statin-induced increases in NO bioavailability and increased NO function through a variety of mechanisms (Adam & Laufs, 2008). Considering the rising levels of obesity and associated lipid disorders in younger populations (National Center for Disease Statistics, 2011) and that women are delaying childbirth until the fourth or fifth decades of life (Heffner, 2004), there is growing clinical interest in being able to treat pregnant women with statins, if required. Indeed, one large randomised multi-centre clinical trial has begun recruiting patients in the United Kingdom to investigate if pravastatin could reduce circulating anti-angiogenic factors associated with pre-

eclampsia (the 'StAmP' trial; Ahmed, 2011). In another recent study published in *The Journal of Physiology*, the fetal femoral vasoconstrictor response to acute hypoxia was assessed under control conditions, and following treatment with a clinically relevant dose of pravastatin (Kane *et al.* 2012). The experiments demonstrated that fetal exposure to pravastatin depressed the fetal peripheral vasoconstrictor responses to acute hypoxia (see Fig. 1). Further, these effects could be prevented in fetal sheep treated with pravastatin under NO clamp conditions, demonstrating that increases in NO levels under pravastatin treatment contributed to the suppression in the femoral vasoconstriction to hypoxia. The data support the hypothesis that statins increase NO bioavailability and oppose neuro-endocrine influences that mediate the peripheral vasoconstriction and metabolic responses to hypoxic stress in the fetus.

At first sight, the results appear concerning given the clinical interest in using statins in complicated pregnancy. Statins may impair the fetal brain sparing response to birth hypoxia. However, the maintenance or increase in cerebral blood flow and, thereby, cerebral oxygen and nutrient delivery, which spares the fetal brain during episodes of hypoxia or asphyxia, is not only dependent on vasoconstriction in the peripheral vascular beds, but also on active vasodilatation in the cerebral circulation. Indeed, this is mediated by mechanisms involving increased NO (Green *et al.* 1996), and several studies have reported a maintained increase in cerebrovascular perfusion during acute hypoxia even in the complete absence of peripheral vasoconstriction, for instance with carotid sinus nerve denervation or α1 adrenergic blockade (Giussani *et al.* 1993). Therefore, in circulations which constrict, such as the femoral vascular beds, enhanced NO bioavailability may diminish peripheral vasoconstriction. However, in circulations which dilate particularly via NO-dependent mechanisms during acute hypoxia, such as the cerebral vascular bed, enhanced NO bioavailability may actually increase cerebral blood flow. Therefore under conditions of fetal exposure to statins or antioxidants, the fetal cardiovascular strategy to defend against hypoxia may change to increase cardiac output and maintain perfusion to most circulations. Clearly, there is an urgent need to assess the impact of antioxidant or statin exposure on changes in fetal cerebral blood flow and oxygen delivery as well as in the fetal peripheral circulations during acute fetal hypoxia. For now, we propose that the use of statins or antioxidants in pregnancy should be considered with extreme caution.

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Honorary Members

The Society awards Honorary Membership to individuals who are held to have 'contributed to the advancement of physiology or to the work of The Society'. This year, we are pleased to elect these six new Honorary Members.

Philippe Ascher

Philippe Ascher graduated from Université de Paris in 1957 with a BA in Biology, earned a DSc in Natural Sciences in 1965 at the same institution, became a Postdoctoral Fellow at the Institut Marey, Paris, 1965-1968. He was Visiting Scientist at Cambridge University, 1968-1969, and at St George's Hospital, 1976-1977, Professor at Universités Paris VI & Paris VII, 1970-2004, and Director of the Department of Biology at the Ecole Normale Supérieure, 1991-2001. He was an Editor of *The Journal of Physiology* from 1977 to 1985. He currently works at Université Paris V (Paris Descartes).

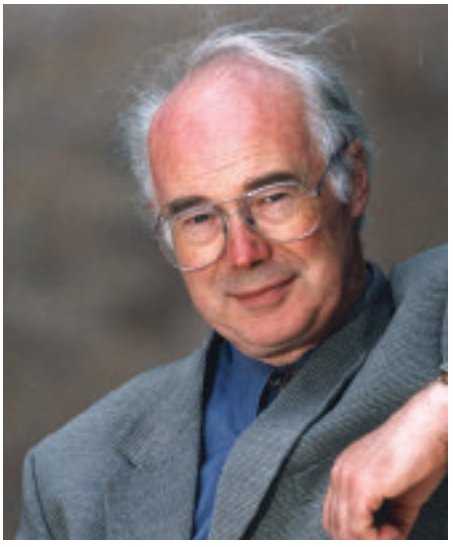
Nominating member of Council, David Brown, said: "Philippe is a very distinguished ion channel physiologist and neuroscientist. He has made many innovative discoveries of crucial physiological importance, most notably perhaps the regulation of NMDA channels by magnesium and glycine. He has had a long career and is still very active in physiological research."

Richard Boyd

Richard Boyd studied for an undergraduate degree at the University of Oxford and completed his medical training in London. He was a research student in Oxford following clinical work in Papua New Guinea and after a period as Senior Lecturer in Dundee, Richard returned to Oxford in 1980, and is currently Deputy Head of the Division of Medical Sciences and Vice-Principal of Brasenose College.

Richard was formerly Chairman of the Editorial Board of *The Journal of Physiology*, Chair of The Physiological Society Council and Senior Secretary of The Physiological Society. He was the 2006/7 GL Brown lecturer.

Proposer, David Meredith, said: "Richard has recently retired from a working life devoted to inspirational teaching and research activity. As well as teaching physiology and medical undergraduates, he has mentored a large number of young researchers through their doctoral and post-doctoral studies, many of whom have gone on to physiology-related careers. In addition, Richard has been a loyal supporter of The Physiological Society and held a number of positions of office. He has been a truly great ambassador for physiology."



Martin Evans

Martin Evans, with Mario Capecchi and Oliver Smithies, won the 2007 Nobel Prize for Physiology or Medicine for developing gene targeting, a technology used to create animal models of human diseases in mice. Studying biochemistry on a prestigious scholarship at the University of Cambridge, Martin earned a BA in 1963, an MA in 1966, and a DSc in 1996, before completing his PhD at University College London in 1969.

In 1981, following his return to Cambridge, Martin successfully isolated embryonic stem cells (ES cells) and demonstrated that these cells could serve as vehicles for the transmission of altered genetic material. This is now the basis of all mouse knockout and targeted genetic manipulation.

He joined Cardiff University in 1999 and received a knighthood in 2004.

Nominating member of Council, William Colledge, said: "Martin Evans was instrumental in developing mouse embryonic stem cells for which he received the Nobel Prize for Physiology or Medicine in 2007. The discovery of ES cells enabled the generation of mutant mice so widely used in physiology."

R Alan North

(Richard) Alan North graduated in physiology (BSc 1969), medicine (MB ChB 1969) and pharmacology (PhD 1973) from the University of Aberdeen. After briefly working as a physician, Alan held appointments as Associate Professor of Pharmacology at Loyola University Stritch School of Medicine in Chicago, Professor of Neuropharmacology at the Massachusetts Institute of Technology, Senior Scientist and Professor at the Vollum Institute of Oregon Health Sciences University, Principal Scientist at the Geneva Biomedical Research Institute (a division of GlaxoWellcome) and Professor of Molecular Physiology at the University of Sheffield. He joined the University of Manchester as Vice-President in 2004, serving as Dean of its Faculty of Life Sciences (2004 to 2008), Dean of its Faculty of Medical and Human Sciences (2006-2011) and founding Director of the Manchester Academic Health Science Centre (2008-2010). His research contributions have been in the understanding of the ionic mechanisms involved in the actions of neurotransmitters and drugs (particularly opiates), and in the molecular physiology of extracellular adenosine triphosphate acting at P2X receptors.

Proposer, David Wyllie, commented "Alan is one of the UK's leading biomedical scientists whose research exemplifies how the disciplines of physiology and pharmacology are so intricately linked. From his early pioneering work studying neurotransmitter and neuromodulator action in the peripheral nervous system through to his studies of P2X receptors his research has been world-leading. For this distinguished research career, which has encompassed both academia and industry, his contributions to *The Journal of Physiology*, as an Editor, and to The Physiological Society, as its President (2003-2006), I am delighted that he has been elected a Honorary Member."

Frances Ashcroft

Frances Ashcroft is the Professor of Physiology at the Department of Physiology, Anatomy and Genetics, Oxford and a Fellow of Trinity College, Oxford. She was elected a Fellow of the Royal Society in 1999. Her research focuses on ATP-sensitive potassium (KATP) channels and their role in insulin secretion, in both health and disease. She is interested in how KATP channel function relates to channel structure, how cell metabolism regulates channel activity, and how mutations in KATP channel genes cause human disease. The ultimate goal is to elucidate how a rise in the blood glucose concentration stimulates the release of insulin from the pancreatic beta-cells, what goes wrong with this process in type 2 diabetes, and how drugs used to treat this condition exert their beneficial effects.

Frances served on The Society's governing Council from 1996 to 2000, and on the *Physiology News* editorial board from 1996 to 1999.

Proposer, Stephen Tucker, said: "Fran's work on the role of the KATP channel in the pancreatic b-cell over the last 30 years has transformed many lives, not just of the many successful scientists who she mentored, but also of the patients who have directly benefited from her work. Her books have also had a lasting impact on the public understanding of science.

"She is a genuine inspiration to all those who interact with her and an excellent role model to both men and women."

Mordecai Blaustein

Mordecai Blaustein's love of physiology was ignited by Howard Schneiderman at Cornell University and nourished at Washington University (St. Louis) Medical School by Daniel Tosteson, under whom he studied the Na,K-ATPase. During his military service in David Goldman's laboratory at the Bethesda Naval Hospital, he investigated anaesthetics in voltage-clamped lobster axons. As an NIH senior fellow with Alan Hodgkin, while studying the squid axon Na pump, Blaustein (with Peter F Baker and Richard Steinhardt) discovered Na/Ca exchange (NCX). This was described in Blaustein's first Physiological Society presentations (1967 and 1968) and led to (1) his proposal that NCX links Na pump inhibition to the cardiotonic effect of cardiac glycosides; (2) his discovery of NCX in arterial smooth muscle; (3) his hypothesis that a ouabain-like compound plays a role in the pathogenesis of hypertension; and (4) the discovery of endogenous ouabain, an adrenocortical hormone.

Rachel Tribe, the nominating member of Council, said: "During his career, Mordecai has made seminal contributions to our understanding of the Na/Ca exchanger and Na,K-ATPase in smooth muscle and the role for ouabain in hypertension. The impact of his mentorship of junior scientists has been inspirational."

Ordinary and honorary members of The Society can propose names for Honorary Membership at any time **www.physoc.org/honorary-membership**

Member profile

A Post Doctorate from Eli Lilly compares their work in industry to that in academia

Siobhan Dennis

Eli Lilly UK

I have spent the last two and a half years working in a Post Doctoral position at Eli Lilly, UK. I was fortunate to obtain this opportunity and want to share my experience with others to increase awareness of this alternative career possibility. The idea of doing a Post Doctorate within an industry was not something I had thought of; in fact, I only came across the idea when the job was suggested to me by word of mouth through friends of friends in the scientific community. However, I was considering where my career would take me and after some traditional 'Google-based research', I felt I could be well suited to research in industry and deemed it would be a great chance to learn some new skills.

The main topic of my project has been to investigate the role of muscarinic receptors in hippocampal network activity. During my PhD I was trained in electrophysiological techniques and I have continued to use these skills within the newly renovated electrophysiology lab. The position is a traditional three years and you still aim to publish in high quality journals. Encouragement to publish extends to the permanent research staff, not just Post Doctorates and students. One of the great aspects of working in industry is that your publications have the opportunity to take on a completely different composition. There is a vast array of techniques performed onsite and this enables a target of interest to be monitored from drug characterisation, to *in vivo* and *in vitro* characterisation and behavioural analysis, making for comprehensive publications. However, it is important to consider the tools you utilise throughout your research, as you do not want to be testing your hypothesis using a drug that could not be mentioned in a publication. What has surprised me the most has been the level of similarity in Post Doctoral projects in industry compared to those offered at a university. The overall aim and scope of my project is exactly what I would have expected to undertake at a university. An obvious, but important difference between university and industry is their research goals; industry employees are driven by drug discovery and it can be difficult to undertake off-topic exploratory experiments experiments that are outside of this remit.

The Centre for Cognitive Neuroscience is a consortium of scientists at Eli Lilly who undertake research in collaboration with six universities in the UK and Ireland. This includes a partnership with the University of Bristol, where I receive advice and project help from my academic supervisor, Jack Mellor. Industries are keen and highly motivated to collaborate with universities and the government, as they value additional input and understand the necessity to delegate to a lab of particular expertise. The more that is understood about a disease and physiological mechanisms, the better the drugs can be targeted and designed, and so basic research is of great importance. The level of supervision is similar to my past experiences in academia, I have regular monthly meetings, but it never feels like you can't pop in and see your boss at any time. However, as most know, the level of supervision received depends mostly on the individual supervisor, rather than the working environment.

A significant benefit of working within a multinational pharmaceutical industry is the

"One of the great aspects of working in industry is that your publications have the opportunity to take on a completely different composition."

access to molecules, including those that you can't get anywhere else and those that can be made on site and to order. This really opens up the projects that you can work on. Although the use of knockout mice is controversial, it can be extremely useful to confirm a targeted drug-mediated effect. Genetically modified mice that have been characterised are often available and can be a useful confirmation tool. In general, companies have a large resource pool, which inevitably speeds up research and data acquisition. From speaking with colleagues within the scientific community, I have observed a slight tension within universities, which has been created by competition and the need to publish first. Within industry everyone works as a team, there is no competition within a single company, only help to achieve your goals. This is a refreshing and friendly environment where everyone helps, and another upside to industry employment.

One major difference I have found between working in industry and academia is all the meetings; there really are endless meetings to go to and successful allocation of your time is imperative. On the upside, everyone is extremely organised and projects are prioritised and experiments are performed in a logical and timely manner. Although every university does have a lot to offer in terms of academic presentations, guest speakers are invited regularly to present onsite and a journal club has recently emerged. There are many more business type meetings to discuss targets of interest and portfolio drugs and, although time consuming, it does give you an experience that you won't get at a university. On the other hand, doing a Post Doctorate at a university you may get more experience in grant writing and application – as a Post Doctorate this is absent in industry. However, if you have a supportive university supervisor you can look to them for advice in these areas.

Here at Eli's Erl Wood facility we have numerous employees with a combined vast knowledge of many techniques. The majority of assays and techniques can be performed onsite or at the HQ in Indianapolis. This is great for producing papers and for developing a better understanding of specific mechanisms of interest and there is always someone who can do something to help your project. However, the only down side is that you aren't required to dabble in any new techniques, as someone more experienced and more capable is always available to do the experiment you may require. Although, if you can find the time, you can always go and watch.

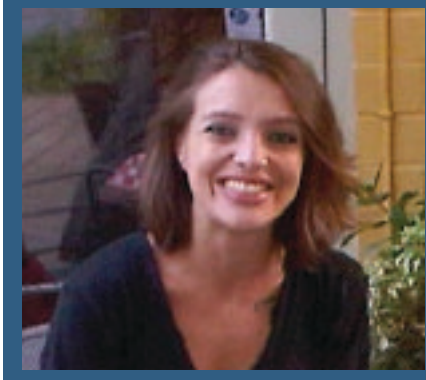
"What I have learnt from dipping my feet in both industrial and academic seas is that, wherever you are and whatever you choose to investigate, you cannot do anything without a good team."

As self-evident as it might sound, being a postdoc in industry is not like being a postdoc in academia. While in academia you might have bucket-loads of ideas but little means to make them real, industry offers you a great deal of resources that you need to transform into data, loads of data. What I have learnt from dipping my feet in both industrial and academic seas is that, wherever you are and whatever you choose to investigate, you cannot do anything without a good team.

Although the Post Doctoral project has been similar to my project experience at university, the projects undertaken by non-students, or non-Post Doctorates, are somewhat different. Projects can come and go quickly and a project can be abandoned at any point if another team finds a significant problem that would prevent continuation into clinical trials. Most work involves drug testing, which could be considered mundane. However, time is found to work on interesting and publishable projects. Day-to-day experimental procedures are different from what I have experienced at university. For example, health and safety is much stricter and it can become time consuming to ensure that you are within guidelines and regulations. You are required to keep good records of your experiments (all of them, regardless of the results) and to write up electronic records for other employees to view. After some resistance, you become accustomed to the procedures and as they are for the greater good they are seen as a great benefit rather than a burden.

Lilly invests heavily in their postdocs, allowing them to do good quality research with some freedom in their projects whilst introducing them to the pharmaceutical world. Last year (2012) around 50 postdocs employed by Lilly gathered from around the world for a one-week trip to a scenic location in Indianapolis, USA. The week before the trip I was apprehensive and concerned about the very full and intensive timetable they had given out. However, after a day of jet lag recovery I understood the value of such an event. The week was tough, challenging and tiring. We learned about different departments and processes involved in drug development and skills that would see us into the future managerial positions. I actually acquired immense knowledge about myself and found that you can push yourself a lot more than you thought! Inevitably, the last night ended in a campfire with marshmallows and much fun.

Although there were the initial jibes of 'turning to the dark side', I still maintain academic connections and I would love to remain in industry as it combines my love for research with my hope to obtain a better understanding of the human biology to aid drug discovery and disease treatment. The past few years I have spent here as a Post Doctorate I have immensely enjoyed. It is a lovely, clean, organised and extremely friendly environment and I feel honoured to have been given the opportunity to work here. I have been surprised by the extensive knowledge and the collaborative nature in pharmaceutical industry and in no way do I feel I have missed out by doing a Post Doctorate away from a university. I speak to my academic supervisor every month and have a yearly retreat with their lab and have benefited by drawing on knowledge of other lab leaders at Bristol. My eyes have been opened to a whole new world of business, health and safety, regulations, legalities, marketing and drug research and this has been a unique and valuable difference to doing my postdoc at university.

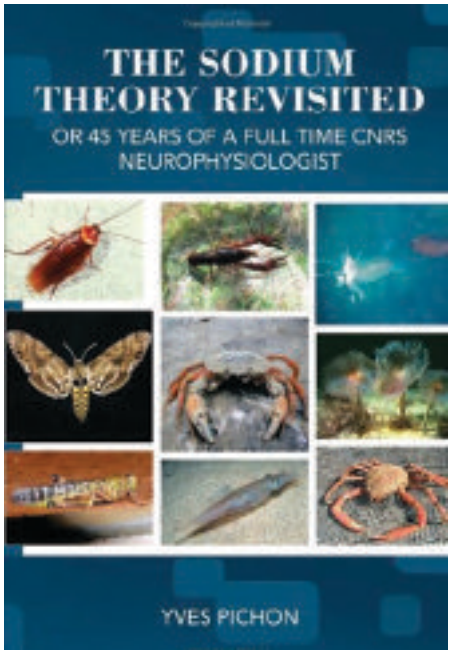


Marie Cotel, also working for Eli Lilly as a post doctorate, shares her experience over the last 3 years.

"As self-evident as it might sound, being a postdoc in industry is not like being a postdoc in academia. While in academia you might have bucket-loads of ideas but little means to make them real, industry offers you a great deal of resources that you need to transform into data, loads of data. What I have learnt from dipping my feet in both industrial and academic seas is that wherever you are and whatever you choose to investigate you cannot do anything without a good team."

Book review:
The Sodium Theory Revisited
(or 45 years as a full time CNRS neurophysiologist)
By Yves Pichon

David Miller



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This is at once an unusual and a strange book. First, it is an example of 'vanity publishing', a rarity in research science. 'Vanity' must seem pejorative, but with the Internet blog as surely the ultimate vanity publishing vehicle not without its merits, this alone is no condemnation. Indeed, for many years there has been a paucity of monographs in our field where distinguished authors describe their ideas, report unpublished work and offer detailed ruminations on their research. The book's title is pregnant with the promise of a consideration of 'the sodium theory' (of nerve excitability) in such a context. Sad to report, Pichon's effort is a bitter disappointment.

Yves Pichon has had a long career in basic neurophysiological research, working almost entirely on invertebrate species. He has collaborated with distinguished neurophysiologists such as Hans Meves, Joan Abbott, John Treherne and many others. As his subtitle confirms, he was a career scientist with the principal French research agency, the Centre National de la Recherche Scientifique (CNRS).

So, is this brief book (fewer than 100 pages in A5 format and dominated by graphs and experimental traces rather than text) a distillate of Pichon's work and science? Well, no. We are offered a series of (often very brief) 'chapters' with promising titles such as: 'The insect Blood-Brain Barrier', 'Osmotic Stress', 'Axonal Membrane Channel Noise'. But these 'chapters' generally contain just a few introductory sentences, sometimes a little methodological detail, one or two results plots … and that's it. It is salutary to note that all the figures (with graphical styles that vary throughout the book) are unattributed. At first glance, one might think these are from the previously unpublished, and thus potentially the more fascinating, 'bottom drawer' findings of a life-long researcher. But, as I too easily established, many (perhaps all?) have indeed already been published. Since there is no acknowledgement for the re-use of these illustrations, I fear the author could have overstepped publishing conventions, at the very least.

But, the niceties of copyright apart, what is spectacularly lacking is any coherent narrative to explain what is being presented to the reader. The promise in the book's title turns out to be entirely empty. The foreword could well be the book's scene-setter, but it is superficial as well as being garbled. (Distressingly, Pichon muddles the temporal relationship of Hodgkin's 1956 [sic] Croonian Lecture to the Royal Society – actually delivered in 1957 and published in 1958 – with Hodgkin's receipt of the Nobel Prize [in 1963]. Yet, two pages later, he has the chronology of all this correct, albeit offering little else of import in the barely 300 words that comprise "Chapter One".)

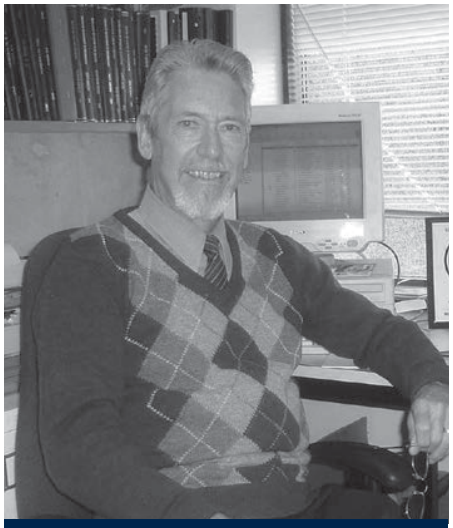
Readers already steeped in the field to which Pichon has valuably contributed might find this random-seeming collection of figures and experiments of interest. But the general physiological reader will find very little to illuminate, divert or reward their attention. As I remarked at the start, this is indeed a strange and unusual book, but ultimately entirely a disappointment.

Would you like to submit a book review to *Physiology News*?

Please get in touch with us on magazine@physoc.org

Joseph Davison

1942 – 2013



Joseph Davison

It is with sincere regret and sadness that we announce the death of Joe Davison. Joe was an outstanding researcher, teacher and mentor. He made important contributions to our understanding of the neural control of the gastrointestinal (GI) tract and its accessory organs. Through his trainees, Joe has had a profound influence on autonomic neuroscience and GI physiology. He continued his career until shortly before his death with a sense of purpose and tenacity, and remained a champion of neurogastroenterology nationally and internationally.

Joe was born in Northumberland and began his scientific career in the UK completing a PhD at the University of Newcastle in 1969 under the supervision of the late Brian Schofield. Davison and Schofield worked on the vagal and enteric control of acid secretion. Joe demonstrated cholinergic and non-cholinergic enteric neuronal reflex pathways in the control of acid secretion. These studies were important as they showed how vagal and enteric control of acid secretion had distinct components and also where they overlapped. A short fellowship in Bristol allowed Joe to develop and pioneer vagal afferent recordings. He continued this work as a lecturer in physiology when he went to the University of Dundee in 1971. In Dundee, Joe's influence on future leaders began. His trainees included David Grundy and Geoffrey Pearson, both of whom have gone on to highly successful academic careers in the UK. Grundy and Davison made pioneering observations on the cardiovascular consequences of vagal afferent activation and, better known, the modulation of vagal efferent discharge by gastric distension and contraction. In this paper, they postulated a reciprocal control of antagonistic vagal motor neurons that innervate the stomach. With Geoff Pearson, Davison moved from his work on neuronal mechanisms in the control of the stomach to consideration of the neural control of the pancreas. The culmination of these studies was a highly significant paper in *Nature* (1981) that showed excitation of the non-cholinergic nerves of the pancreas stimulates amylase secretion by a different intracellular coupling mechanism from that activated by cholinergic nerves or by cholecystokinin (CCK), gastrin or bombesin. Whilst in Dundee, Joe also studied the sensitivity of vagal afferents to chemical and mechanical stimuli that also included the earliest recordings of the action of peptides such as CCK on vagal afferent terminals (with G Clarke).

In 1982, Joe left the UK being recruited as Professor and one of the first 'Medical Scientists' of the newly created Alberta Heritage Foundation for Medical Research (AHFMR) to the University of Calgary. In Calgary, he continued pioneering studies of both secretion and neural control mechanisms throughout the GI tract. In Calgary, Joe made important observations on gallbladder motility (with Eldon Shaffer), continued studies on non-cholinergic control of pancreatic and salivary secretion and continued with themes of neuronal circuitry in GI motor and secretory control in general. Again, one cannot overstress the importance of his laboratory as a permissive environment for trainees. Joe's trainees in Calgary included Mary Perdue, Beverley Greenwood Van Meerveld, Christine Bear, Fiona Boissonade, Bengt Gustafsson, Ron Mathison, Gillian Shillabeer, Kathy Fraser (Reynolds) and Keith Sharkey. All of them have gone on to successful faculty positions in Canada, the UK, Sweden and the USA. In total, three of Joe's trainees have gone on to win Janssen (Master's) Awards at the AGA, illustrating well the nature of Joe's impact on the field.

In Calgary, Joe's scientific contributions continued unabated. He made important theoretical and practical contributions to the field when, in 1984, he published an account of the innervation of the GI tract in a book edited by J Christensen and D Wingate. In this chapter he outlined how the hierarchical innervation of the gut worked, including important observations on vagal and sympathetic control. These concepts are now fully incorporated into the field, and appear in textbooks and teaching materials. In a long-standing collaboration with R Mathison, Joe discovered and patented a series of novel anti-inflammatory peptides derived from salivary glands.

In his later years, Joe made important contributions to Australian Neuroscience. With Ashley Blackshaw and his PhD student Penny Lynn he helped develop techniques to record from murine colonic afferents which led to a number of novel findings. On subsequent visits to Australia, working with Gino Saccone, Joe became part of his lab at Flinders University, and brought together a team, again pioneering recordings from afferents *in vivo* and *in vitro*, this time from the pancreas. Together these projects generated the concept that pain sensing fibres were consistently found on blood vessels, not in ductal or gut tissue.

Taken together, Joe has had a very significant impact on the development and growth of digestive sciences in Canada, the USA, Australia and the UK through his many and varied research contributions and by providing an outstanding training environment. Throughout his career he published over 180 peer-reviewed papers and about 50 book chapters and reviews.

Beyond his contributions to research, graduate and postgraduate education, Joe held leadership positions in Canada and internationally. He was Head of Physiology at University of Calgary for 10 years (1988-1998), Chair of Canadian Council on Animal Care (2004-2005), Co-Editor of the *Canadian Journal of Physiology and Pharmacology* (1991-1998), Chair, International Society of Autonomic Neuroscience conference (2003), and on the editorial boards of a number of prominent journals, including the *Journal of Gastrointestinal Motility* and *The Journal of the Autonomic Nervous System*.

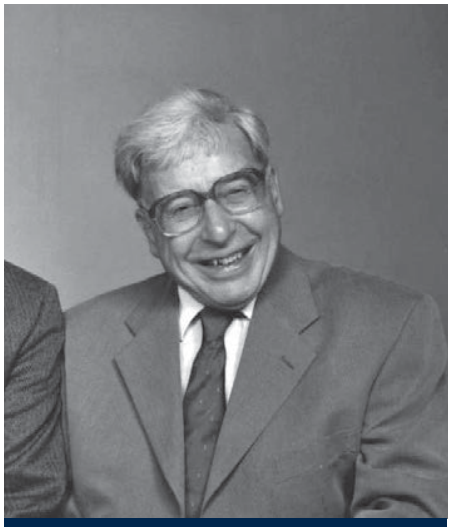
Joe is survived by his wife of over 40 years, Mary, his two children, Sara and Christopher, and four grandchildren.

Ashley Blackshaw, David Grundy & Keith Sharkey

In Joe's memory, the Dr Joseph S Davison Memorial Scholarship has been created at the University of Calgary to assist graduate students in gastro-intestinal physiology. Donations may be made online at https://netcommunity.ucalgary.ca/davisonaward

Bob Edwards

1925 – 2013



Bob Edwards

Recording for 'Reunion' at BBC Radio 4

Many obituaries of Bob Edwards have appeared in the few weeks following his death early on the morning of 10 April 2013. These set out his many qualities and achievements fulsomely and (almost) comprehensively. As I write this personal reflection five weeks after his death, there is one feature that I personally miss most about Bob not being 'here'. It is a feature that was barely mentioned by others (nor in an earlier piece in *Physiology News* by Richard Gardner written to mark the award of Bob's Nobel prize) and by focusing on it here I hope to eliminate the 'almost'.

I first encountered Bob in 1966 as he entered the Part 2 teaching room (now the Hodgkin Huxley Seminar Room) of the Physiological Laboratory at Cambridge to give us the first of eight lectures on Advanced Topics in Reproduction. I had little anticipatory enthusiasm, for the Part 1 lectures (not alas given by Bob) had been uninspired and full of ground squirrels, rabbits and lots of steroid biochemistry – with barely a mention of humans to pique the interest of an aspiring medical student like myself. As I recall it, Bob was (characteristically, as I was later to discover) a few minutes late and as he rushed in apologising he dropped his lecture notes and then gathered them up – apparently in random order – inconsequentially as it happened as he rarely seemed to consult them! After eight weeks of being variously challenged, irritated, impressed and amused by his futuristic vision of a reproduction that encompassed endocrinology, immunology, cell biology, ethics, developmental biology, politics, population studies, his beloved genetics and PEOPLE, I was hooked and inspired! And so I shelved my clinical course at Charing Cross Hospital and commenced a PhD with him that autumn – to the horror of most of the then academic staff in the laboratory who made it very clear that they considered Bob a 'lightweight' who worked on a distasteful subject ('down there' – as they put it), not an elevated one like the nervous system, and who – horror of horrors – actually spoke to the press and public about his work! Indeed, he was quietly delighted at the ironic twist that when the department was renamed recently; neuroscience took second place to development!

Bob was accustomed (as I was soon to find out) to this intellectual and social snobbery, which he greeted with his characteristic laugh and a smile. And it is that laugh that I miss so much, because that laugh became very familiar and reassuring over the years. However many travails that he faced, he never seemed to lose either his sense of proportion or his sense of humour. However bitter the attacks on him, however hurt he must have been, however desolate at his patients' disappointments over those long years until Louise Brown was born, and the even longer years until his achievements were recognised with the award of the Nobel Prize in 2010, he was always able to muster a smile and a laugh – sometimes rueful, sometimes hopeful, but always warm and affectionate, and never at any one else's expense. Bob's laugh reflected his care for us all – his students, his patients, his colleagues, his family, his ideas and his world. The world is a much sadder place without it.

Martin Johnson

The Society also regrets to announce the deaths of:

Annie B Elliott

Vahe Amassian

Notices and full obituaries can be found The Society website at www.physoc.org/obituary-notices

The Journal of Physiology

Summary of AGM presentation made by David Paterson, EiC.

- *The Journal* remains the most highly cited journal in physiology, and 2012 saw the number of full text downloads exceed 5 million. *The Journal* continues to rank well in all citation metrics, and has a cited half-life of over 10 years
- Overall submissions continue to rise year on year, and the acceptance rate is currently at approximately 28% for original research articles
- The time from submission to first decision is currently the lowest it has been over the last few years, and we are now able to publish copyedited and typeset versions of articles in under 46 days. All research articles continue to be published online within a week of acceptance
- In order to engage the readers of *The Journal* we have introduced 'CrossTalk' articles that raise the profile of physiology and stimulate debate
- *The Journal* continues to have a presence at major international meetings in order to target authors from specific audiences
- Plans for the future include:
  - Developing new media initiatives
  - Reducing the time from submission to first decision
  - Reducing acceptance rate to our target of 20%
  - Targeting under-represented research areas
  - Establishing a pipeline of Topical Reviews and Invited Content

Early Investigator Prize winner

The Journal of Physiology is delighted to announce that the winner of the Early Investigator Prize 2012 is Rahul Agrawal (University of California, USA) for his article: 'Metabolic syndrome' in the brain: deficiency in omega-3 fatty acid exacerbates dysfunctions in insulin receptor signalling and cognition. Please visit The Journal website for more details on the prizes, including the names of the two runners up.

Physiological Reports

From left: Susan Wray, Thomas Kleyman, Philip Wright and Martin Frank

Physiological Reports, the new journal jointly owned by The Physiological Society and the American Physiological Society, continues to make progress since the publication of the first research article on 7 May. By the end of August 60 papers had been published. The European launch took place on Monday 22 July at the IUPS meeting in Birmingham. Several hundred people came along to listen to speeches by Philip Wright, the CEO of The Physiological Society; Susan Wray, the Editor-in-Chief; and Martin Frank, the Executive Director of the American Physiological Society. The Editorial Board met for the first time the following day. Going forward the Board will meet twice a year, at EB in April in the USA and at the main meeting of The Physiological Society in the UK in early July.

The Editor-in-Chief, Susan Wray, commented at the end of August:

'I'm really pleased to say that already we have had almost 200 submissions to *Physiological Reports*. This vindicates the case for the new journal. There is a need to have a first class, open access outlet for papers in the entire range of physiology. With *Physiological Reports*, authors know their work will be seen, and, importantly, recognised to have had full peer review. If you have not submitted yet why not take a look at the papers we have already published and give your Society's newest journal a try?'

Another reason to publish in *Physiological Reports* is the fast publication time. For the papers published by the end of August (excluding those delayed by a technical issues), the mean time from submission to publication was 61 days, consisting of 31 days from submission to acceptance and 30 days from acceptance to publication.

Physiological Reports is disseminated using the continual publication model, each article published online as soon as it is ready. But each article is also assigned to an issue, and going forward, the issues will be closed at the end of each month, with an e-TOC (table of contents sent out by email) and Editor's Choice at this point, creating a monthly journal for those who like publication the traditional way.

Experimental Physiology

Editor-in-Chief, Paul McLoughlin, addressed Members at The Society's Annual General Meeting in July. He told Members:

- The number of submissions to *Experimental Physiology (EP)* continued to increase throughout 2012 as did the citations to the journal and full text downloads of journal articles
- Journal metrics showed that *EP* had maintained its position amongst its main competitor journals, despite a slight drop in the 2012 Impact Factor. It continued to perform particularly well in the immediacy index, ranking ninth out of 79 physiology journals
- The move to online-only in January saw the successful implementation of several new features – mobile optimized site, new findings summaries, free online colour, a commentary feature, and introductory videocasts. These have been well received and early indications are that dropping print has not adversely effected readership numbers
- The speed of review has improved in 2013 with *EP* returning an initial decision and two referees reports on average within 32 days (compared to 37 days in 2012) of submission. Accepted articles are published 'In press' within five working days of acceptance and published in final copy-edited version in <6 weeks of acceptance

The Physiology and Pathophysiology of Obesity

This themed issue is being produced in conjunction with The Society's 2013 Topic Meeting. For further information and a preliminary call for papers see ep.physoc.org/site/includefiles/prelimcall.xhtml

The Editorial Board welcomes new consultant Editor


Gareth Leng

Gareth Leng is Professor of Experimental Physiology and Head of the School of Biomedical Sciences at the University of Edinburgh. Although first trained as a mathematician, he is best known for his experimental studies on neuroendocrine systems; his research has covered diverse aspects of the regulation of vasopressin, oxytocin, growth hormone and appetite regulation, and more recently computational modelling studies. He is a former editor-in-chief of *The Journal of Neuroendocrinology*, and is President of the executive of the International Neuroendocrine Federation. Gareth will also act as a liaison editor with *Physiological Reports*.

***Experimental Physiology* is proud to be publishing lectures given by the following at IUPS:**

- Denis Noble, President's Lecture: Physiology is rocking the foundations of evolutionary biology
- Leon Kreitzman and Russell G Foster, Annual Public Lecture: The Rhythms of Life – What your body clock means to you
- William Catterall, Sharpey-Schafer Lecture: Structure and function of voltage-gated sodium channels at atomic resolution
- Geoffrey Burnstock, Paton Prize Lecture: Purinergic signalling
- Eleanor Maguire, Joan Mott Lecture: How are memories represented and recollected by the human brain?

Now published at ep.physoc.org


Eleanor Maguire

Early Career Author's Prize

Winner:
Editor in Chief McLoughlin presented *Experimental Physiology*'s Early Career Author's Prizes at IUPS to Marcia Abbott, University of Southern California, Los Angeles, CA, USA

For: AMPKα2 is an essential signal in the regulation of insulin-stimulated fatty acid uptake in control-fed and high fat-fed mice. Marcia J. Abbott, Silvana Constantinescu and Lorraine P. Turcotte. *Exp Physiol* **97** (5), 603-617; doi.10.1113/expphysiol.2012.064402

Runner up:
Richard M. Bruce University of Birmingham, Edgbaston, Birmingham, UK

or: Muscle afferent activation causes ventilatory and cardiovascular responses during concurrent hypercapnia in humans. Richard M. Bruce and Michael J. White. *Exp Physiol* **97** (2), 208-218; doi:10.1113/expphysiol.2011.061606

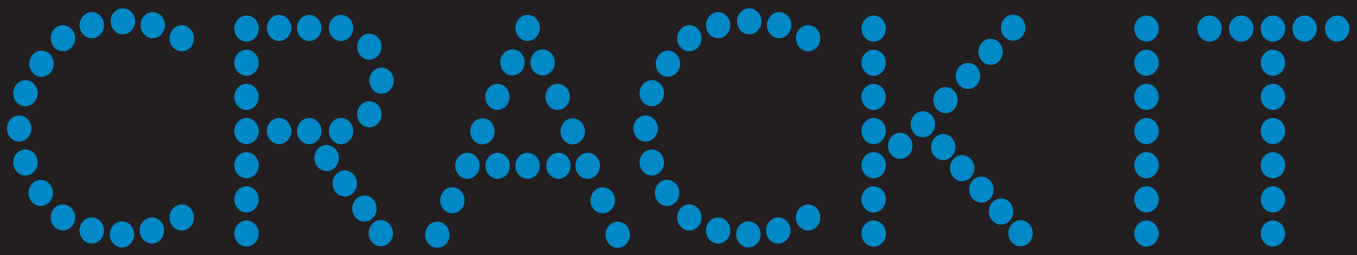
CRACK IT Challenges competition

The 2013 NC3Rs CRACK IT Challenges competition is now open. CRACK IT Challenges is a milestone-driven funding competition from the NC3Rs which is designed to minimise the use of animals in research and support the development of marketable products and/or improved business processes. This year the Challenges are funded by the NC3Rs, the Technology Strategy Board and Alzheimer's Research UK with in-kind contributions from the Challenge sponsors.

Each of the five Challenges offers up to £1m funding, a research contract for up to three years and in-kind contributions such as data, compounds and expertise from sponsors.

For 2013, there are five Challenges: UnTangle, Inhalation Translation, InPulse, NephroTube and Virtual Infectious Disease Research.

The competition is run in collaboration with the Small Business Research Initiative (SBRI) and the deadline for applications is 12 noon on 6 November 2013. More information can be found at www.crackit.org.uk or by emailing CRACKITenquiries@nc3rs.org.uk.



The Physiological Society
Hodgkin Huxley House
30 Farringdon Lane
London EC1R 3AW
United Kingdom

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020 7269 5710
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