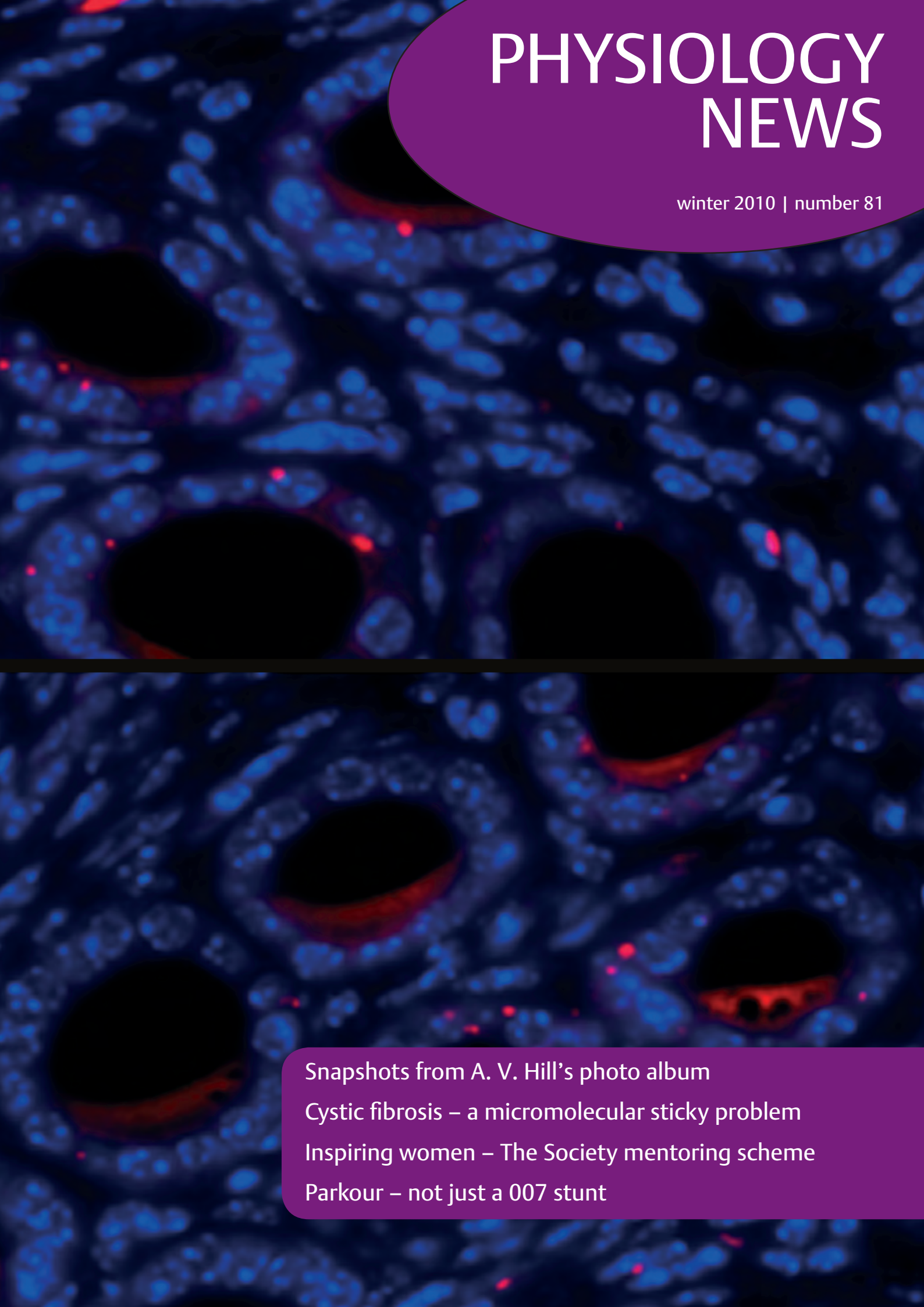

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winter 2010 | number 81

Snapshots from A. V. Hill's photo album

Cystic fibrosis – a micromolecular sticky problem

Inspiring women – The Society mentoring scheme

Parkour – not just a 007 stunt

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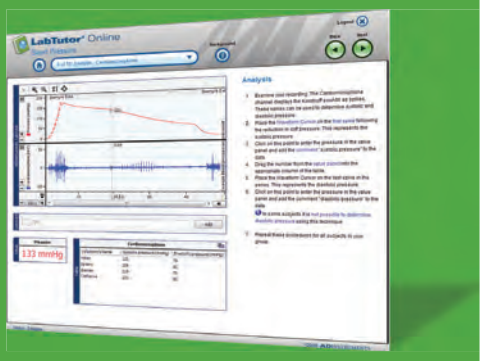

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The Society's dog. 'Rudolf Magnus gave me to Charles Sherrington, who gave me to Henry Dale, who gave me to The Physiological Society in October 1942'

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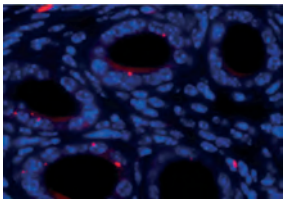
The Physiological Society

Advancing the science of life



Cover image: Mucus retention in uterine glands +/– HCO_3^-, p.37.

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Action points

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

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Physiology News

Deadlines
Letters and articles and all other contributions for inclusion in the Spring 2011 issue, No. 82, should reach the Publications Office (magazine@physoc.org) by **13 January 2011**. Short news items and letters are encouraged, and can usually be included as late copy if space permits.

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

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Guidelines for contributors

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

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

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

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

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

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

In this issue

Welcome to the final *Physiology News* of 2010.

Summer conference season seems to get ever longer, and now lasts well into September. We have another crop of conference reports this time (pp. 4–12), including one on the Festschrift for former *J Physiol* Reviewing Editor Bernd Nilius.

History – of which conferences form a part, certainly in science – can sometimes be brought alive by a photographic image. On p. 17 Bill Van der Kloot takes us for a fascinating rummage through A.V. Hill's photo album. We also have an in-depth interview with ion channel pioneer Bertil Hille (p. 13), including some reminiscences of the greats of early post-war electrophysiology.

Given what some people see as the ever-growing dominance in science of molecular biology, it is pleasing to see that several of the scientific features in this issue have a human physiology theme. There cannot be many physiology magazines that can boast the science of James Bond (p. 29), spaceflight (p. 32) and phantom limbs (p. 34) in the same issue! We also continue our popular Methods series with an article I am tempted to sub-title 'Everything you always wanted to know about Western blotting (Part 1)' (p. 46).

In the present economic climate, engagement by scientists with the wider world is assuming ever greater importance. We have an extended section this issue detailing some of the outreach work carried out by Society members (pp. 53–57). And engagement goes beyond simply talking about science – see the Science is Vital rally report on p 50, or Simon Singh's discussion of the scientific debate-chilling effect of England's libel laws on p. 22.

Last but not least, it is a special pleasure to applaud the award of the 2010 Nobel Prize for Physiology or Medicine to Professor Bob Edwards, long-time member of the Cambridge Physiological Laboratory. His pioneering of IVF exemplifies how basic science can change the world – politicians please note (p. 12).

Austin Elliott
Editor

Smoke signals... or just smoke?

These remain uncertain times for UK physiologists. The results of the UK Government's Comprehensive Spending Review (CSR) were announced last month. So now that the dust has settled – if it has – is the picture any clearer?

I should note first that, between the summer and the CSR, we saw perhaps the most concerted campaign of recent times by the UK science community to seek to mitigate the likely scale of the cuts. The learned societies, UK industry, university heads, leading scientists, political figures and science journalists all lobbied hard to get across to the Government that science is a key engine of progress and prosperity. A special mention has to go the Science is Vital campaign, masterminded by a small group of working scientists [1]. They managed in only a few weeks to conjure up both a petition with over 35,000 signatures, and a rally of 2000 people in London outside the Treasury which gained considerable media coverage (see p. 50). There seems little doubt that this campaign, and the other representations made to the Government, allowed Science Minister David Willetts to argue for science to be at least partially spared.

However, despite that, the result is still cuts. They are far less bad than had been feared, but the 'cash freeze' on the UK science budget announced in the CSR amounts to a progressive annual cut of somewhere around 2–3%, year on year, over the next four years. This is better than the 15–20% cuts (over four years) that had been widely trailed, but it still means less grants funded, less postdocs and less PhD students.

It is also necessary to say that we still do not know many of the details. Evan Harris, the former MP and science advocate, published a useful checklist on his *Guardian* blog as 'Don't Be Spun on Science Funding'[2]. So far it seems clear there will be large cuts to capital spending, so most infrastructure projects – e.g. new university laboratories – will be on hold for several years. The new UK Medical Research Centre at St Pancras will go ahead, but other national-level projects are likely to be cut. Research spending by other ministries is also likely to be cut, though this is perhaps less worrying to biological science than to engineering and technology. English universities outside the South East are also likely to take a science funding hit from the abolition of the Regional Development Agencies.

The detailed share-out of funds between the different research councils also remains unknown. Overall though, it seems absolutely inescapable that grant funding rates, already well below 20%, will fall further, with even more high-alpha rated grants going unfunded. Many commentators predict the research councils will respond by focussing more overtly than ever on 'priority areas', or by setting up mechanisms to prevent serially unsuccessful applicants from applying for funding for some subsequent period of time.

The other looming iceberg for university science in the UK is the major changes set to be imposed on the funding for university teaching. Large cuts to the university teaching budget are to be coupled with legislation to raise the cap on tuition fees to £6–9K pa, in line with the recommendations of the recent Browne Review on funding tuition. Though some direct funding for undergraduate teaching in 'strategically important' subjects like science will remain, student fees will become the major source of teaching income.

Although the research and teaching funding streams are notionally separate, the separation is artificial, given that most university academic staff do both. Falls in academic staff numbers are widely predicted as universities struggle to make savings. Staff will thus be under pressure to deliver 'more for less' in teaching, just as in research. And meanwhile, the universities in which scientists work will be undergoing changes on a scale not seen in many decades. None of this is comforting news.

How does what the UK is doing compare with its competitors? Here again, things are less than rosy. UK R&D (research and development) spending before the cuts was already less than in many developed countries. As science policy specialist Bob Ward explains on the *New Scientist's* 'S Word' blog [3]:

"According to the OECD's [Organisation of Economic Cooperation and Development's] latest figures, government-financed gross domestic expenditure on R&D by the UK was 0.54 per cent of Gross Domestic Product in 2008. This was less than the OECD average of 0.64 per cent, and markedly lower than the corresponding figures for Canada, France, Germany and the US. It was also less than the 0.63 per cent recorded for the UK in 1995."

This is not a cheering picture and raises two issues. The first is whether there will be a 'brain drain' of scientists out of the UK to other countries where the funding situation is less grim – for instance, Germany is actually set to *increase* science funding. The second issue is whether there is any prospect for increasing funding in the UK if the economy picks up. Many science policy commentators have noted rather pointedly that the Treasury, the most powerful UK Ministry and 'gatekeeper' to funding, is the only ministry *not* to have a Chief Scientific Adviser. Some see this as symptomatic of a failure by the Treasury to appreciate the key role science plays in the economy. Ward notes:

"[UK Science minister David] Willetts will need a lot of help over the next four years to convince the treasury that more should be invested in science and research. The research community must assist him by demonstrating clearly that such an investment will improve our international competitiveness, and increase the nation's long-term prosperity and well-being."

So how can scientists help with this? The success of the Science is Vital campaign suggests that science does have political pull, if it can organize itself to use it. So maybe it is incumbent on us to keep showing the politicians all the ways in which science is important.

This is not, note, a call to write more hyperbolic and inaccurate press releases about the future implications of research, still less overblown 'projected impact statements' of the kind that annoy people on grant application forms. It is, though, a call to all academics to think about how research – their own and others' – in the field they work in has impacted on the world. Concrete examples play far better with politicians than sweeping statements – and these concrete examples are the tools that science ministers need to convince the Treasury.

I imagine quite a few UK-based readers wrote to their MPs about Science is Vital. That was a good thing. Perhaps now is the time to write them the *next* letter.

Austin Elliott

[1]http://scienceisvital.org.uk/

[2]http://www.guardian.co.uk/science/political-science/2010/oct/20/1

[3]http://www.newscientist.com/blogs/thesword/2010/10/

Cellular and Integrative Neuroscience Themed Meeting, London, 6–8 April 2011

From neurones to networks: birth, death, disease and repair of the nervous system

Where will you be able to watch the construction of the tallest building in the European Union? Have a pint in London's only surviving galleried coaching inn? Grab your lunch in the best food market in London? Get locked up in jail as well as participate is a world-class neuroscience meeting? The Guy's Campus, King's College London, that's where.

Neuroscience is a broad subject that requires a significant depth of understanding and added to this, it is at present a very fast moving field. The symposium will provide three days of symposia covering some major areas of neuroscience in depth. These will be accompanied by oral communications and poster sessions. The evening before the meeting starts there will be the Hodgkin–Huxley–Katz Prize Lecture given by Roger Nicoll to appropriately kick things off. The first day of the meeting will cover 'Development of the nervous system' in a symposium organised by Andrew Lumsden; following this 'Circuits to synapses' which will be overseen by Ian Thompson and Juan Burrone. On day two we move on to 'Degeneration of the nervous system' organised by Jean Marc Gallo and sensibly following this Pat Doherty has a session on 'Regeneration of the nervous system'. Day three and Jack Prince with Carmine Pariante are running 'Cellular modelling of neural development and disease' which is followed by 'Transcriptional and epigenetic regulation in neurological, neurodegenerative and psychiatric disorders' organised by Noel Buckley and Jonathan Mill.

Key note presentations will be interspersed with oral communications and we predict lively poster sessions on days 1 and 2. So, as you can see, there is something for everyone and a lot for many. Topics that will be covered include neurogenesis, neuronal stem cells, signalling pathways, depression, schizophrenia, neurodegerative disease and psychiatric disorders, to name a few. The special interest groups that are particularly relevant to this meeting are Blood–Brain Barrier, Cellular Neurophysiology, Cellular Signalling, Development and Plasticity, Ion Channels, Neuroendocriology, Sensorimotor Control, Sensory Functions and Somatosensory Physiology. However, we think all physiologists will find much of interest – after all the nervous system controls all that we do.

The venue is the Guy's Hospital Campus, now located in the 'London Bridge Quarter', King's College London. The location is served by one mainline rail station (London Bridge) three tube stations (London Bridge, Borough and Monument) and 24 bus routes. If you register on line you can use a Boris Bike (first 30 minutes is free!). The new South Bank has a plethora of restaurants, pubs, hotels, art and entertainment, so the evenings will be as busy as the days.

So clear your diary, submit your abstract(s), book your train tickets and get you accommodation arranged so that you can see all 310 metres (over 1000 feet in imperial units) of the Shard being built, have a pint (or two) in the George Inn, grab a snack in Borough Market, escape from the Clink and get an update on the state of Neuroscience in 2011.

Jon Robbins, Pat Doherty and Jeremy Ward

Cardiac & Respiratory Physiology Themed Meeting, Birmingham 1–3 September 2010

A 3-day Themed Meeting on Cardiac & Respiratory Physiology was held in Birmingham in September 2010, with a focused symposium on hypoxaemia – 'Coping with hypoxaemia: strategies and solutions'. The meeting was divided into five sessions (O_2 sensing mechanisms, blood flow regulation, lessons from comparative studies, intermittent hypoxia and chronic hypoxia) that gave an insight into research on the strategies for coping with hypoxia in a wide range of animals, through the mechanisms of hypoxia sensing, to hypoxaemia-associated diseases. Some personal highlights are given here.

The first day focused on cellular responses associated with exposure to hypoxia, predominantly hypoxic pulmonary vasoconstriction (HPV) and oxygen sensing by the carotid body. The different hypotheses for oxygen sensing were presented: whether the primary mechanism of carotid body activation was through oxygen-sensitive voltage-gated K^+ channels (e.g. the $K_V4.3$ subtype) (T. Perez Garca, Universidad de Valladolid, Spain), mitochondrial metabolism (Jeremy Ward and Keith Buckler, KCL and Oxford) or AMP kinase activation (Mark Evans, Edinburgh) were discussed in detail. This debate continued through to the Early Career Scientists' Session on the last day of the meeting although no firm conclusion was reached, even after the stimulating (and often heated) discussion by

Lord Mayor of Birmingham, Len Gregory (left) and Stuart Egginton, scientific organiser of the meeting.

Left, Luc Teppema, Leiden University Medical Center, The Netherlands and (right) George Balanos, University of Birmingham, UK, scientific organiser.

Stephen Archer (Chicago), and Jeremy Ward on whether the 'redox hypothesis' or the 'mitochondrial hypothesis' was correct. It was agreed, however, that more consistency between the P_{O_2} levels used in experiments was needed to explain some of the differences seen between labs, and the physiological relevance of oxygen tensions used to mimic chronic hypoxia was questioned. The roles of these mechanisms in fetal growth restriction (FGR), which is also caused by hypoxia, were discussed and Uzo Sampson (Manchester) showed that although the causes of HPV and FGR may be similar, the mechanisms, especially with regards to K_V channels, are not.

The comparative physiology session on the second day began with a fascinating talk by Bill Milsom (British Columbia) on adaptations to hypoxia in a bird that migrates at high altitude, the bar-headed goose. These adaptations include their more effective ventilation which involves slow and deep breathing, producing less dead space in the lungs. In these geese, oxygen availability and utility is enhanced by their high-affinity haemoglobin, greater muscle capillarity and increased mitochondria compared with other species. Tobias Wang (Aarhus) followed with his talk on how reptiles cope with hypoxia by mixing oxygenated and deoxygenated blood in two-chamber hearts, a real feat of flow control by variable resistances. Göran Nilsson (Oslo) described the mechanisms of survival under anoxia by crucian carp, which initially change their gill structure in response to hypoxia to increase the surface area for oxygen diffusion. High glycogen stores in muscle, and the ability to convert excess lactate produced by anaerobic respiration into ethanol, which is released into the environment, then supports long-term survival in anoxia. Carp also increase the production of the endogenous tranquiliser, GABA, which reduces their activity and

preserves energy. These clever mechanisms of survival in hypoxic conditions have hopefully inspired biomedical scientists to try and transfer these mechanisms for manipulation in humans at high altitude, although survival on a similar regime of 'drugs and alcohol' may be questionable!

The afternoon's talks were varied, from students' talks on hypoxia-induced reduced glucose sensitivity in the isolated whole carotid body, to the mechanisms of intermittent hypoxia-induced sleep apnoea, and the ability of hypoxia to cause respiratory muscle weakness as a result of increased muscle plasticity. The day ended with a talk by Janice Marshall (Birmingham) on local mediators of acute and chronic hypoxia in muscle, with particular reference to adenosine metabolism and its contribution to endothelium dysfunction, leading to cardiovascular disease in adult life. High altitude was the subject of the day, and at the Society Dinner that evening held at the National Sea Life Centre in Birmingham, Chris Imray (Coventry) gave an excellent after-dinner presentation on his experiences carrying out hypoxia research on Mount Everest. He described the extremely difficult, emotional but ultimately successful experiences his team encountered on their journey. If only they were bar-headed geese...

The final session of the meeting began with a talk by Andy Cossins (Liverpool) challenging current ideas on myoglobin as an exclusively muscle protein, as it also exists in brain and in the vasculature of fishes. Asif Ahmed (Edinburgh) described the protective effects of haemoxygenase in pre-eclampsia (another disease associated with low oxygen content), and the possibility of a novel use for the anti-cholesterol drug simvastatin in clinical therapy for hypoxaemic diseases.

There were two plenary lectures. Peter Barnes (Imperial) presented non-antibiotic macrolides or combination therapy of theophylline and steroids, as an alternative to steroid-only treatment in steroid-resistant diseases such as chronic obstructive pulmonary disease (COPD) and in asthmatic smokers, where oxidative stress caused by cigarette smoke promotes excessive inflammatory protein synthesis. Nanduri Prabhakar discussed possible carotid body-mediated mechanisms whereby the intermittent hypoxia that occurs in sleep apnoeic patients might give rise to a plastic change in chemoreceptor function leading to elevated blood pressure.

The talks were interspersed with poster sessions and coffee breaks that allowed one-on-one discussions between early-career and established scientists. Particularly useful was the Point–Counterpoint session held at the end of the meeting, which demonstrated the need to challenge one another's ideas to further our knowledge and understanding. Well-deserved poster prizes were awarded to Melissa Brereton (Manchester; see below) and Andrew Holmes (Birmingham). All in all, a thoroughly enjoyable meeting, in a fantastic canal-side venue in central Birmingham – with good catering too!

Fahima Syeda
Birmingham University

More from an early-career scientist

The second Cardiac and Respiratory Physiology Themed Meeting, 'Coping with hypoxaemia: strategies and solutions', with an impressive array of keynote speakers and sessions dedicated to early career scientists, was the ideal forum to present my research to leading experts away from the intimidating arena of some larger meetings.

Many of the keynote speakers at this meeting performed the early pioneering work elucidating the mechanisms of oxygen sensing and blood flow regulation in the systemic and pulmonary vasculature. Although not strictly cardiac or respiratory physiology, my PhD research investigates the regulation of blood flow across the human placenta by oxygen-sensitive potassium channels. As our understanding of these processes in the placental vasculature is at an early stage, using the existing knowledge of other vascular beds is crucial in advancing this field. To gain expertise and advice from these internationally renowned scientists whose research I have admired and am inspired to replicate, was an opportunity not to be missed!

Embarking upon a research career as a young scientist in a research field filled with many controversies can be a daunting prospect. One highlight for me was the Point–Counterpoint early career scientists' session which helped alleviate these fears somewhat and emphasise that these controversies are real. They do not result from inexperience or a lack of understanding of the subject area. One of the steepest learning curves we have to try and overcome during the transition from an undergraduate student to an independent scientist is accepting that research is not black or white. There is a multitude of ways to interpret a biological mechanism or phenomenon. The real skill young scientists have to learn is to formulate an opinion based on the available evidence, question and generate exciting new research questions. Although this skill is not as easy as learning a new technique in the lab, I think more meetings such as this one that include debate sessions and encourage active exchange of ideas would motivate and inspire the next generation of scientists.

I thank The Physiological Society for allowing me to present my research at this meeting and awarding me the prestigious Physiological Society Poster Competition Prize. I highly recommend young scientists to attend meetings such as this in the future as it was a thoroughly enjoyable and beneficial experience.

Melissa Brereton
University of Manchester

Festschrift in honour of Bernd Nilius

From 22 to 24 September, researchers from 20 countries gathered in Leuven (Belgium) for 'TRP 2010: TRP channels, from structure to disease'. This meeting was organized on the special occasion of the 65th birthday of Bernd Nilius, founder of the Laboratory of Ion Channel Research at the University of Leuven, former Reviewing Editor of *The Journal of Physiology*, and one of the leading figures in the ever-expanding field of TRP channel research.

TRP 2010 participants in front of the Leuven town hall.

After a good night's sleep following the well-appreciated get-together party with Belgium's premium products (Trappist beers and cheese), the 145 participants met at the medieval Grand Béguinage for two exciting days filled with accounts of today's TRP channel research in all its facets (featuring 15 invited speakers), vivid and open discussions and amusing anecdotes about Bernd Nilius' career and personality.

Day 1 started with molecular detail of TRP channel function, with Rachelle Gaudet (Harvard University) presenting data on the crystal structures of intracellular domains of TRPV channels and their role in channel regulation, and Giovanni Appendino (Università del Piemonte Orientale A. Avogadro) providing a chemist's view on natural products as potent TRP channel ligands. Stuart Bevan (King's College London) then presented a new animal behavioural assay to pin down the contribution of TRP channels to cold sensing, thereby settling some long-standing disputes in the field.

The physiological roles of the Ca^{2+}-activated TRP channels TRPM4 and TRPM5, in particular in the cardiovascular system and the pancreas, formed the topic of the lecture of Rudi Vennekens (University of Leuven). René Bindels (Radboud University Nijmegen) provided a nice overview of the function and regulation of the epithelial Ca^{2+} and Mg^{2+} entry channels TRPV5/6 and TRPM6. Reinhold Penner (University of Hawaii) started his lecture on TRPM2 with a brilliant, touching and extremely funny foreword on the connections between Bernd Nilius, Leuven, Father Damian, Molokai and the selectivity filter of TRP channels. Somewhat unruly, Ardem Patapoutian (The Scripps Research Institute, La Jolla) presented a completely TRP-free lecture about the recent discovery of Piezo1 and Piezo2, which probably form (part of) the long-sought mechanically activated cation channel.

Bernd Nilius answering questions after his 'final' lecture.

Day 2 started with Lutz Birnbaumer (NIEHS at Research Triangle Park), who presented data to support his controversial view on the role of TRPC channels and Orai proteins in store-operated Ca^{2+} entry. Next, Gary Lewin (Max Delbrück Center for Molecular Medicine, Berlin) revealed his unpublished work on the role of TRPV4 as a peripheral osmosensor, and Thomas Gudermann (Ludwig-Maximilians-Universität München) showed the dramatic effects of loss of TRPM6 function in mice. David Clapham (Children's Hospital, Boston) not only discussed the role of TRPC5 in fear-related behaviour, but also pinpointed some important open questions in the TRP channel field, including Bernd Nilius' further career planning.

In addition to the invited lectures, there were also two vivid poster sessions, with a total of 36 posters. The poster presented by Michael Poteser (University of Graz) on the importance of calcium permeation through TRPC3 for induction of NFAT signalling in cardiac myocytes was awarded the poster prize.

The last afternoon started with Sven-Eric Jordt (Yale University) describing the role of TRPA1 as a detector of environmental chemicals by the respiratory system, and its contribution to the development of asthma. Using the fruit fly as a model, Craig Montell (Johns Hopkins Institute, Baltimore) drew molecular parallels between the visual system and regulation of thermosensitivity. Dan Cohn (Cedars-Sinai Medical Center) gave a clinical view on the variety of TRPV4 gene mutations that cause bone deformation diseases, thereby illustrating the high medical relevance of basic TRP channel research. Finally, the celebrant himself spoke about the 'irritating nature' of TRP channels, referring not only to the role of these channels as sensors of irritating chemicals, but also to their complex, mind-boggling and poorly understood biophysical properties. At the end of his inspiring lecture, Bernd Nilius even performed an hilarious live experiment – a modern version of EH Weber's silber Thaler illusion – to directly 'prove' the mechanosensitivity of TRP channels. No better way to demonstrate that good science and great fun can go hand in hand.

The organizers would like to thank *The Journal of Physiology* and The Physiological Society for their generous financial support of TRP 2010. Look forward to the Bernd Nilius festschrift in *The Journal of Physiology*, to be published early in 2011, presenting symposium reviews by five of the invited speakers.

Thomas Voets
University of Leuven

The biomedical basis of elite performance

All eyes will be on Britain in 2012, as London plays host to the Olympics. To celebrate the achievements of these elite athletes, and to showcase world-leading sport and exercise-related medicine, physiology and pharmacology research, The Physiological Society and the British Pharmacological Society will host a three-day sports science and medicine meeting at The Queen Elizabeth II Conference Centre, London from 19 to 21 March 2012. This meeting will be supported by *The Journal of Physiology*, *Experimental Physiology*, the *British Journal of Pharmacology* and the *Scandinavian Journal of Medicine and Science in Sports*. All four participating journals are published by Wiley-Blackwell.

The meeting will comprise symposia, oral communications, posters and plenary lectures, all of which will focus on basic and applied scientific and medical issues of direct relevance to athletic performance. Furthermore, to increase the impact, all invited speakers have agreed to contribute a manuscript to be published prior to the meeting across the participating journals.

More specific details about the meeting will follow in due course. However, to kick start this exciting venture we will be publishing a series of Olympics-themed articles. As Chair of the Scientific Programme Committee for the 2012 Games meeting I have agreed to contribute the first of these articles.

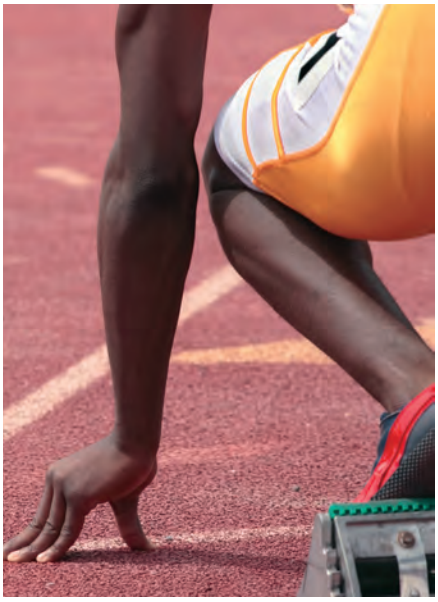
Paul Greenhaff
Chair, Scientific Programme Committee, School of Biomedical Sciences, University of Nottingham

Professional athletes are commonly taking non-steroidal anti-inflammatory drugs during periods of intense training. But just because these drugs aren't banned by the World Anti-Doping Agency, does that mean they're worth taking?

Non-steroidal anti-inflammatory drugs (NSAIDs) are a class of non-prescription drugs (i.e. freely available over the counter) that exert anti-inflammatory and analgesic effects by inhibiting cyclo-oxygenase (COX) isozymes, the rate-limiting step in the formation of prostaglandin, and by doing so reduce musculoskeletal pain. These drugs are not included in the World Anti-Doping Agency's list of banned substances and therefore can be used by athletes, perhaps most frequently during intensive periods of training when injury, inflammation and pain are most common.

As one might expect, athletes are frequent users of NSAIDs. Approximately 25% of those competing at the Sydney 2000 Olympics reported NSAID use in the three days before random drug testing (1). While large scale use of NSAIDs might reflect the physical cost of elite athletic training, additional data point to athletes' potential misuse of open access to these substances (2,3). Specifically of concern is the *prophylactic* use of NSAIDs for extended periods with the aim of minimising pain and injury and thereby enabling training loads and adaptation to be maximised.

NSAID use is on the increase in top level sport (2), perhaps because the performance-related stakes are getting higher. This latter point is emphasised by the recent publication of Garnham (4), which reported that about 50% of a sample of elite (world class) athletes confirmed they would take an undetectable illegal substance if it guaranteed them an Olympic gold medal, even if they were aware that it would kill them within five years! Interestingly, no data appear to be available that show NSAID use by elite or recreational athletes reduces injury prevalence or improves muscle and exercise performance. However, there is a body of evidence documenting clear adverse effects of NSAID ingestion on cardiovascular, gastrointestinal and musculo-skeletal systems, particularly with prolonged use. Moreover, in the context of maximising muscle training adaptation, it has been known for some time that the increase in muscle protein synthesis normally seen following eccentric exercise is blunted following NSAID ingestion (5).



Ironically, inflammation as the result of intense athletic training may actually work to an athlete's advantage. A role is emerging for exercise-induced inflammation *stimulating* positive adaptive responses in skeletal muscle. It is known from gene transcript profiling that a single bout of resistance exercise (particularly eccentric exercise, i.e. lengthening contractions) induces inflammatory gene responses in human quadriceps muscle (6), and that these inflammatory responses are maintained when a second bout of eccentric exercise is performed (7).

Animal studies have shown increased expression of the pro-inflammatory cytokine IL-6 (8), and the myogenic transcription factors Myf-5 and MyoD (9), in muscle following lengthening contractions. Given that IL-6 has been shown to promote satellite cell-mediated hypertrophy in isolated

muscle cells (10), these findings collectively point to augmented myogenic growth factor expression and satellite cell proliferation – occurring secondary to muscle inflammation – as mechanisms by which resistance training might induce *augmented muscle mass and strength gains* over time.

It has recently been demonstrated that the anti-inflammatory effect of prostaglandin blockade inhibits muscle satellite cell proliferation following acute eccentric exercise in humans (11). In keeping with this, McKay *et al*. (12) recently demonstrated a clear association between increased muscle IL-6 levels and satellite cell proliferation in humans after a single bout of eccentric exercise. What is not yet clear is whether these responses persist with training, thereby potentially underpinning augmented muscle adaptation.

It seems there is a distinct possibility that, contrary to popular opinion, prophylactic use of NSAIDs may actually *impair* muscle adaptive responses to resistance training and blunt athlete performance development, which brings into question the merits of prophylactic use of NSAIDs for extended periods of time. Clearly this warrants further investigation and has significant implication for issues beyond athletic adaptation, such as the loss of skeletal muscle with ageing.

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Gordon Research Conferences

An invitation to speak at a Gordon Research Conference (GRC) affords a unique opportunity that is not available at more conventional conferences such as Society for Neuroscience or Physiology Society meetings thus, when I was invited to attend the *Glial Biology: Functional Interactions among Glia and Neurons* conference which was held in Ventura, CA last year, I had no hesitation in accepting. Although GRCs offer an air of exclusivity since the opportunity to present at a GRC is by invitation only, there are a limited number of places available for graduate students and post-docs. Before describing the highlights of this conference, a brief history of these unique conferences may be enlightening.

History

The first official Gordon Research Conference took place in 1931, but the idea of an annual series of conferences had been germinating for a couple of years in the mind of Dr Neil E. Gordon, a chemistry professor at Johns Hopkins University. At around this time Johns Hopkins University was pioneering research-based chemistry education, and the Chemistry department was at the cutting edge of translating theoretical chemistry into applied research. This led to seminars being held in the summer to present new findings in the field of chemistry, which visiting scientists as well as graduate students could attend. Although a series of informal chemistry meetings had been held in the summer at Johns Hopkins University, Gordon instituted a more formal conference format. It was Gordon's intention that these seminars would focus on an individual topic per conference and provide an opportunity for small groups of scientists working at the frontiers of a particular aspect of research to come together and discuss in-depth aspects of the most recent advances in the field, and to stimulate new directions for research. From 1931 to 1947 the conferences were held in the

The three living Directors (left to right): Alex Cruickshank, Nancy Ryan Gray and Carlyle B. Storm.

Chesapeake Bay region of Maryland, but moved to Gibson Island in the mid 1930s. Although Gordon moved to Central College, Missouri, the conferences continued to be run from Johns Hopkins. Fortuitously, Gordon had become secretary of the American Association for the Advancement of Science (AAAS), and thus the AAAS took over management of the conferences and Gordon became the official director of the conferences in 1939. Untouched by the escalating war in Europe, in 1941 eight separate conferences were held, at which point larger premises on the island were purchased. In 1942 Gordon moved to become chair at Wayne University Chemistry department and he relinquished directorship in 1945. In 1947 the AAAS appointed W. George Parks as director and moved the conferences to Colby Junior College in New Hampshire. Under Park's directorship the conferences continued to expand and by their 25th anniversary four thousand scientists attended thirty-six conferences. In 1956 GRC became an independent non-profit organisation devoted to scientific and educational purposes. Parks resigned in 1968 and his deputy Alexander Cruickshank took over. This was a period of enormous expansion of the GRC with the number of conferences and attendees doubling under his leadership. The meetings remained on the East Coast until 1963, when they expanded to Santa Barbara, CA on the Pacific Coast. In 1980 the West Coast venue moved to Ventura, CA, about one and half hours north of Los Angeles, and in 1990 the first conferences were held outside of the USA. Cruickshank was instrumental in encouraging conference chairs to apply for external funding and federal grants for the purpose of subsidizing speakers and keeping costs down for attendees. On Cruickshank's retirement in 1993 he had devoted 47 years to the GRC, 25 as director. Carlyle B. Storm succeeded Cruickshank, and the expansion of GRC continued with conferences held in Tuscany, Oxford, Japan and Hong Kong. In 2002 GRC moved its headquarters to West Kingston, Rhode Island and on Storm's retirement in 2003 directorship was taken over by Nancy Ryan Gray, who remains the current director. That there have been only five directors in the GRC history goes a long way to explain not only the success, but also the stable format of the conferences.

Format

A key aspect of the conferences that has remained unchanged since their inception is that they last five days. The initial conferences were billed as summer courses, which ran from Monday to Friday with the conference season lasting five weeks, and each conference focusing on a specific topic. Current conferences now run from Sunday night until Friday morning with the daily schedule encompassing communal breakfast, presentations in the morning, afternoon free, communal dinner, followed by evening presentations. The afternoons usually contain informal discussion groups organised at the conference, for in-depth discussion of specific topics. In order to avoid the distractions that are an unavoidable hazard of

The harbour at the site in Ventura at the Four Points Sheraton.

conventional conferences held in urban areas, GRCs are intentionally held in remote locations. There is an emphasis on the presentation of unpublished data, which hopefully will engender helpful discussions about the progress and direction of future studies. Unlike many other conferences, abstracts or conference proceedings are not published.

Growth of conferences and attendees

Since their inception over 600,000 scientists at over 5,500 conferences have attended GRCs, and currently, over 25,000 scientists attend the 200 or so annual conferences (the average number of attendees is 140 with attendance ranging from 110 to 200 maximum).

Although the original conferences were focused on the topic of the initiator, chemistry (in the initial years the conferences focused on topics such as x-ray crystallography, organic chemistry and colloidal chemistry), the scope of the conferences has expanded, encompassing not only the life sciences, but also the physical sciences. It is a sign of the times that conference topics now include renewable energy.

The number of conferences and attendees continues to grow from the initial few conferences per year at East Coast locations. This was most noticeable under the stewardship of Alex Cruickshank who encouraged a more decentralised financial approach to the conferences, which allowed the chairs of conferences to apply for external funding, which in turn allowed greater subsidy for speakers and graduate students. The contribution of students and post-docs is a key aspect of the conferences. While the GRCs try to maintain the number of participants as small enough to promote full participation and discussion, they must also be large enough to support the diversity of participants from professors to students.

The GRCs are keen to encourage attendance of post-graduate students and post-docs, and at some GRCs a pre-meeting symposium is arranged, which takes place on the Saturday and Sunday before the meeting, with attendance limited to graduate students and post-docs. These new Gordon Research Seminars (GRS) are designed to provide a stimulating and non-intimidating environment for graduate students and post-docs to present their research in talks and poster sessions. There were 19 of these in 2009, 28 in 2010 and there will be 52 in 2011, with the numbers expected to increase. GRCs offer students an opportunity to not only hear experts in their field present, but also to interact with them on a relatively informal basis. Such opportunities are strictly limited at other conferences.

Glial Biology: Functional Interactions among Glia and Neurons

This conference was chaired by Professor Bruce Ransom, University of Washington, with Professor Philip Haydon, Tufts University, acting as vice chair. This is the 4th such conference, the initial one being chaired by Gerry Dienel in 2003. It is an indicator of the momentum of glial research that such a conference is not only viable, but that it encompassed a very broad range of topics. The sessions were:

Form and functions of synaptic-glial interactions

Lessons learned from flies and worms

Glial regulation of neurogenesis, neural migration and neural plasticity

Glia and ischemic brain injury

Glial control of CNS vasculature and the brain–blood interface

Glia and information processing

Microglia and CNS pathology

Metabolic interaction among neurons and glia

Molecular pathophysiology of gliomas and dysplastic glia.

Given the remit of GRCs not to report on unpublished or preliminary data, I will limit my discussion to published data and highlight a few notable presentations.

In the 2nd session David Featherstone, University of Chicago, presented an astonishing talk based on studies in *Drosophila* in which mutation of a glutamate cystine transporter altered the mating behaviour of male flies. Normal male flies will mate only with female flies, but male flies with a reduced expression of the transporter, named genderblind, will attempt to court male flies as well as female flies, thus exhibiting bisexual behaviour. In the recently published article Dr Featherstone hypothesised that glutamatergic synapse strength mediated the genderblind phenotype, based on experiments

in which the glutamate antagonist DGG eliminated bisexuality in the genderblind mutants, and conA, a glutamate receptor agonist that inhibits desensitization, induced bisexual behaviour in the wild type male flies. Imagine a similar situation in humans! In a personal communication Dr Featherstone related how he had been inundated by calls from worried parents seeking advice on how to 'fix' their homosexual children.

I was initially disappointed that Maiken Nedergaard, Univerity of Rochester, chose to change her talk from astrocytic buffering of potassium as I was hoping to pick up some novel information for undergraduate lectures. However, her replacement lecture was fascinating – a comparison of the morphology of astrocytes from humans and rodents. Maiken's talk, based on a recent publication, illustrated, not surprisingly, that human astrocytes exhibited a far more complex morphology than rodent astrocytes, but additionally demonstrated that human astrocytes display overlapping regions, not seen in rodents, and conduct Ca^{2+} waves faster than the rodent. In addition, human astrocytes were shown to have similar morphologies to primate (macaque monkey and chimpanzee) astrocytes. It is interesting to note that on a morphological basis there is very little that distinguishes human layer 5 pyramidal cells from an equivalent rodent cortical neurone, suggesting that the enormous complexity of the human brain function compared with the rodent may at least in part be due to the complexity of astrocytes. After all, Einstein had a higher density of cortical astrocytes than mere mortals.

In the final session, at least from a clinical point of view, was perhaps the more interesting talk. Harald Sontheimer, University of Alabama, described his experiments based on a recent publication, on the role of ion channels in brain tumour metastases. Harry described experiments that showed how blocking Cl^- channels inhibited brain tumour development. The theory behind this work is that in order for tumours (which are nearly all of glial origin in the brain) to invade neighbouring tissue in the brain, which is composed of densely compacted cells, the tumour cells co-localise a Ca^{2+}-activated K^+ channel and a CIC-3 Cl^- channel in the invading processes. The activated channels release K^+ and Cl^- and water follows, resulting in cell shrinkage, which facilitates tumour invasion via the narrow extracellular space. Blocking the Cl^- channels with chlorotoxin reduces cell volume decrease, which hampers tumour cell invasion. Chlorotoxin is now in Phase III clinical trials and shows great selectivity for gliomas.

The next Glial Biology conference is scheduled to take place from 6 to 11th March 2011 in Ventura, CA. I strongly encourage any PhD students or post-docs working in the field of glial research to consider applying for attendance at the conference. The GRC website (www.grc.org) contains information on up-coming conferences, application and registration procedures, and information for students and post-docs. A separate website (www.frontiersofscience.org) is dedicated to the first 75 years of the GRCs and contains a treasure trove of information, including memories of distinguished GRC participants. A related publication 'Reflections from the Frontiers' is available from Amazon.com.

Angus Brown

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2010 Nobel Prize

The much-deserved Nobel Prize awarded to Professor Bob Edwards [1] marks the culmination of one of the great stories of late 20th century physiology and medicine; the years of painstaking work that culminated in the birth of the first 'test tube baby', Louise Brown, in 1978. It is a pleasure to welcome his honouring by the Nobel Committee.

The award of the Nobel Prize for the discovery of IVF (*in vitro* fertilisation) by Edwards and his clinical collaborator, Patrick Steptoe, perhaps throws into sharp relief some of the recent debates about 'blue skies' research – and the need for research to be perceived as cutting edge, or to have 'economic impact'. Edwards was a basic researcher in a university Physiology department, and the IVF work was preceded by many years of lab work on animal, as well as human, oocyte physiology and fertility. The IVF work was not 'fashionable' at the time; the focus in fertility research in the 1960s and 70s was on reducing fertility, and Edwards and Steptoe had to scrabble for funding. Notably the MRC, then the major British funder of medical research, declined to support Edwards and Steptoe's work in 1971 on ethical grounds, though a fascinating recent historical paper reveals the reasons behind the decision were far more complex [2]. Following the MRC's decision, Edwards and Steptoe's work continued with private money, notably from the USA, until Louise Brown's birth triumphantly vindicated them. The 4 million plus children born by IVF since Louise Brown, and now the children of those children, are eloquent testimony to Edwards' vision and perseverance.

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What makes ion channels exciting – a penetrating interview with Bertil Hille

On a recent trip to Seattle Angus Brown took the opportunity to catch up with Professor Bertil Hille in the Department of Physiology and Biophysics at University of Washington. Bertil is one of the founding fathers of modern membrane biophysics.

Angus Brown (AB): Could you tell us where you did your undergraduate and PhD degrees?

Bertil Hille (BH): I was an undergraduate at Yale University studying Zoology, but I also took a whole series of courses called Biophysics, so I could have had a degree in Biophysics as well. Then I went to Rockefeller University in New York City where the degree was called Life Sciences and graduated in 1967 after 5 years. It was a very advanced and modern environment where there were many professors and a few students, so we could make up our own programme.

AB: Your father was a famous mathematician at Yale, who wrote numerous textbooks. What influence did he have on you?

BH: My father was a role model for a quiet academic. He was totally involved with his mathematics and other intellectual things. What I got from him included how to think hard and steadily and not having to have entertainment while thinking about science. He also was a role model with respect to having written 14 books in his lifetime, and so that made it very natural for me to write a book and feel, half-way through my career, that that was the appropriate thing to do.

AB: You worked with Alan Hodgkin for a year as a post-doc, in 1967–8. What was that experience like?

BH: Alan wrote to me a few months before I went that his laboratory was full and he was fully preoccupied, so it would be best if I came a year later. Well, it wasn't really in my plans to come a year later so I went anyway, and he was actually fully preoccupied. At the time Hodgkin, Mordy Blaustein, Peter Baker and Rick Steinhardt were discovering the sodium–calcium exchanger in squid giant axon. Mordy Blaustein was to work with Hodgkin in Plymouth on

Bertil Hille

the squid, and Hodgkin was a person whose focus was so total that he couldn't think about another thing at the same time. I was basically put in another room and didn't have much exposure to Alan during that time. Richard Keynes realised that I knew about electricity and I could measure electrical things, so by the time I had been a post-doc with Alan Hodgkin for maybe a month and a half, really being told to work by myself, Richard Keynes had acquired me so I spent the rest of the year in Richard Keynes' lab working with Larry Cohen. In fact, after the squid season was over, Alan Hodgkin said there was no place in his lab for me, I had better do a theoretical problem. Since I had no theoretical problem in mind, when Richard Keynes said, "Why don't you come to our lab in Babraham", that seemed like a much better prospect.

AB: And you weren't given any squid – you were neglected?

BH: It was hard to get the squid. It seemed like Hodgkin and Blaustein should have the squid, and they were the ones who gave out the squid. I got some, but it was hard for me to even learn how to open a squid. Trevor Shaw came from London and he was very nice and helpful. He showed me the dissection and helped me get some apparatus while I was there in Plymouth.

AB: So there are no hard feelings obviously but it's not the best way to set out on your career is it?

BH: I learned that that was not a way I would like to work with post-docs and it helped me to be a better and more sympathetic post-doctoral advisor [in Bertil's 42 years at the University of Washington he has supervised 46 postdocs and 18 graduate students].

As an aside Bertil showed me a letter sent to him by Marni, Hodgkin's wife, after Hodgkin's death. She wrote: "But he (Hodgkin) followed your career with great interest and latterly with a faintly disapproving feeling that you were writing too much and experimenting too little, but then experimental scientists always do feel like that."

AB: One aspect of ion channel history has always puzzled me and I may be wrong in this, but if we think of the first generation of modern researchers in the field of neuronal excitability, Cole excluded, they were predominantly British: Hodgkin, Huxley, Katz (German working in Britain) and Lord Adrian, but the next generation were almost exclusively American: you, Clay Armstrong, Bill Catterall, Richard Aldridge and numerous others. Why do you think the British influence so dramatically dissipated?

BH: I think you're quite right and this is a very interesting sort of science/sociology issue. There are quite a number of factors I could identify which I think weigh equally. One was that Hodgkin, Huxley and Katz had all felt that the excitability problem had been solved and finished. So when the papers were published in 1952, they thought that there was nothing more to do and they projected that to anybody who talked to them. They got rid of their amplifiers and they each turned, very productively, to other fields. It meant that they felt they had finished – the Hodgkin and Huxley

papers were so alarmingly new and different and hard to accept that people outside had no idea what to do next either. So it was a surprising time in science when papers had a giant impact and nobody had any idea what we could do further. Then another factor would be, I'll speak about Hodgkin particularly, that Alan Hodgkin had almost no research students. Richard Keynes was one, and he continued the excitability question in Britain. His agenda was to study everything except electricity about excitability, so he studied light, heat and isotopes. The only other student that I know of Alan Hodgkin's is Peter Stanfield. Thus, there is this big hiatus where Hodgkin, Huxley and Katz produced almost no research students meaning there were no new PhDs developing their ideas in Britain. As an anecdote I can tell you that while we were not able to get squid in Plymouth, Alan Hodgkin told me that he was annoyed at training Americans who then all went back to America with his good ideas and continued to work on them. Now what he really meant was that Great Britain had no system for post-doctoral support. So in the laboratories of Huxley, Katz and Hodgkin there were post-docs from the United States mostly, and a few from Germany, but not from Great Britain. This meant that they produced no progeny. It was a mistake in respect to advancement of science that in Britain there was no post-doctoral support system. That kind of programme did not exist, and it existed quite completely in the United States even for people to leave the United States with money to do their work in other countries. But we shouldn't forget though that there was also Otto Hutter in London who Denis Noble worked with, so Denis Noble carried the banner for the cardiac side of excitability, and Denis Hayden was in Cambridge and was studying the gramicidin channel. I think Hodgkin and Huxley are so unusual that you don't expect to have them repeated ever again, neither in Britain nor in America nor anywhere else [laughs]!

AB: Your early work had a significant modelling component. How important do you think modelling is in the field of ion channel biophysics?

BH: I continue to model all the time so to me it's very easy. I still am conscious of the feeling of many biologists that it's too easy to model: if you have several parameters, you can make an elephant wag its tail. At the same time I find it very satisfying to make models. I think the models are like a physical explanation of things using whatever concepts as far as they can go – often just kinetics, so you don't quite know what the molecules are, or if you do know the molecules, it is still at some simplified view of them as charges and as dipoles. But in the end you can show that a certain class of thinking does work to explain your phenomenon. Hodgkin was very clever about it in many of his papers. For example, when Hodgkin and Keynes measured isotope fluxes in potassium channels and people now say that they showed it was a long pore, Hodgkin would write instead that "the system behaves like one in which there was a long pore through which particles were moving." That's quite different from the strident words, 'strongly proves that such and such', which people think is a good way to express their belief in some scientific conclusions.

AB: You were the first to coin the phrase 'ion channel'. How did you come to your views on channels selective for sodium and potassium?

BH: We can go back to Hodgkin first. He was making models in the sense that there is no discussion of molecules, except for water, and sodium, potassium and calcium, and ATP. He wasn't a chemist who thought about what a molecule looks like or what its chemical properties are. He said to me that he and Andrew Huxley were disappointed in the results of their papers because they had thought they would be able to describe the mechanism. In the end they felt that their model was just a model and didn't prove that the mechanism was correct, which they state in the last paper, "there's nothing about our equations that says this is the right thing". Now for me, I was a student at Rockefeller University and we had studied and memorised all the enzymes and intermediates of intermediary metabolism. We knew that there were hundreds of enzymes and hundreds of genes. I was impressed that all of biology used proteins; for each job there was a different protein each with its own specificity. The enzymologists were purifying these proteins and could study them in the test tube one at a time, and show that they had different amino acid sequences and different properties and different active sites. That was the background that I came to the excitability problem with, thinking that for every biological function there would be some series of proteins, each one specialised for an individual job. I just thought, without even knowing any experiments, that there would be sodium channels and potassium channels and calcium channels that would serve those functions and they would be different molecules and one could study them just as the biochemists studied the enzymes. I also thought they should be pores.

AB: So it was just intuitively obvious to you that there would be selective proteins for each ion?

BH: I think it was just a frame of mind. It wasn't probably very thoughtful. It was just that I came to biology at that point from the point of view that it's going to be protein pores that are specific. Now Clay Armstrong who is 6 years older than I am, was already, just a year before I started, working with squid giant axons in Cole's lab in Woods Hole and he was very clearly beginning to write in the same framework, so Clay and I were I think fully parallel and in full agreement even though we didn't spend a lot of time together talking about it.

AB: You were working independently.

BH: We were independent. But we had exactly the same point of view. And I think we, cynically, had exactly the same negative feelings about the other people who had a different point of view.

AB: When you came to Seattle in the late 1960s a colleague tried to dissuade you by calling it an 'intellectual desert'. It's very hard

AB: to believe nowadays, 40 years later. What was the department like when you joined it?

BH: It was the Department of Physiology and Biophysics; it was extremely strong as one of the best in the country. It took 14 or 15 students each year, which is a fantastically large number, so it had 45 students at any moment and if you look at the list of students you'll see that each year, 4 or 5 people who we know well came in who are now chairs and professors who have to do with ion channels and electrical excitability. There was a very significant interest in excitability.

AB: Could you tell us a bit about the computer aspect as one of the attractions?

BH: I made a tour of a few schools on the East Coast and mostly schools on the West Coast looking for a job, and since I had used a voltage clamp with a computer in my graduate studies I felt that it was necessary to have a computer online to make the use of voltage clamp reasonable. Almost every school had no idea what an online computer would be. So this was far and away the only and most knowledgeable department with respect to online computing. They said, yes, I could use their computer on Saturdays. So I did all my experiments for the next 10 or 15 years on Saturdays.

AB: You were the first researcher to record electrophysiological data using a computer: how important was this as an advance in routine lab studies?

BH: Instead of having to take a week to analyse the data you could do it in minutes. I'd say anybody who was patch clamping today and not given a computer would be alarmed. You would never want to photograph a million single channel openings and try to analyse them from measurements on a film.

AB: So you effectively wrote the prototype for Axon pCLAMP?

BH: Yes, except in the beginning I had an analog way of making the pulses, so I personally would turn a dial, which I arranged to click in steps so that you got particular voltages. I controlled the experiment by turning the dial and the computer recorded whatever happened. Only later was it possible to actually have the computer generate the voltages.

AB: You've mastered a variety of techniques including the ability to build your own amplifiers and oscilloscopes, computer programming, knowledge of enzyme kinetics, chemical radii, electrophysiological recordings from nodes and various other techniques. Moving on to the 21st century, what skills do you think are essential for students entering neuroscience?

BH: Well now if neuroscience means things that I'm interested in, that is cellular electrophysiology of neurons and of ion channels, then I would say that everything modern has to be done. It's patch clamp now. Although you don't have to know how to build the amplifier anymore, you have to learn about Ohm's Law and capacitors and you have to be able to think about what the amplifier is doing. When I first saw that Erwin Neher was able to do patch clamp, before they published their famous paper, I came back and built five and I gave one to Peter Detwiler just to get people interested in it. I think microscopy and imaging have become our 'new and essential.' Confocal microscopy is already fairly old but it's essential. Newer forms: FRET (fluorescence resonance energy transfer), TIRF (total internal reflection microscopy), and continually new forms of microscopy are things that you'll need to bring in. Next is molecular biology, the ability to stitch together alterations of genes and to express them in cells, typically in cell lines. But if a neurobiologist really does neurobiology, you have to express them in real neurons, either knocking down expression or expressing mutants. Very successful in the last 10 years is to knock out a gene in a mouse and then to study the cells in which you have re-expressed a mutant form of the same gene to ask what part of the molecule's doing what thing and what it's for.

AB: Why do you think the sodium channel hasn't been crystallised yet?

BH: Most of the ion channel crystals are bacterial proteins partly because you can grow so much material and because the molecules of bacteria are not glycosylated. If you have glycosylation, which is like cotton, it's hard to pack proteins together in a regular structure. Instead there's some springiness and you get an irregular crystal but it's not good enough to get a structure. So neither the sodium channel nor the calcium channel has been crystallised.

AB: Your research changed tack in the mid 1980s when you started to focus on signalling via G-protein-coupled receptors in both excitable and non-excitable cells so what prompted this change in direction?

BH: It was very consciously taken. I had written my book, published in 1984, and that allowed me to review all of my life because most of the chapters in my book were something I had done sometime or other. The book was written because I felt that biophysicists were moving too far away from biology and were writing papers that were incomprehensible to other fields like structural, chemical, developmental and cell biology. We needed the input from all those people to help us realise the significance and mechanisms of ion channels. Looking at the book, I felt too that I needed to turn my work towards more biological questions. So instead of asking how many tenths of an Angstrom the hole in the sodium channel was, I would try to get what I perceived to be how hormones acted on cells. That was G-protein-coupled receptors, basically things that affected mood and all the outputs of the whole autonomic nervous system. So it was a real change for me, I felt somewhat naked and delicately exposed while I didn't know much about those fields.

AB: A lot of your studies were in non-excitable cells.

BH: As an undergraduate zoologist I was interested in all kinds of biology, which could be in kidneys or muscle, so it seemed to me that the significance of ion channels, and the significance of G-protein-coupled receptors, was as great in all other cells as it was in neurons. There was no need to focus on neurons. I never have truly regarded myself as a neurobiologist, you know. I have

studied ion channels and cells and how the cell membrane negotiates passing ions through it, but I've never used more than one cell at a time in a dish. I've never had a two-cell preparation, which means that you can't do too much neurobiology!

AB: Could you tell us how you came to write your book '*Ionic Channels of Excitable Membranes*', and how it evolved over the subsequent editions? I have a personal interest in this in that the 1st edition of your book came out in 1984, and as an undergraduate in Dundee in 1985 I was given that book as part of our course by Jim Elliott. In fact, your book was a major influence in steering me towards a career as an electrophysiologist, which 25 years later I still am.

BH: I had come to the point of feeling that the biophysicists were not talking in a vocabulary that was good for talking to other biologists. Yet I knew that we had lots of exciting discoveries, starting with Hodgkin and Huxley, and that papers as brilliant as Hodgkin and Huxley's were almost unreadable to most of the people who I wanted to know about this exciting research. I wanted to find a way to tell people about the basic discoveries and what was known without having to envelop it with excess physical and theoretical baggage. I was inspired by my father's having written textbooks before. So I wrote a book in which the first chapter was easier, and the second chapter was a little less easy, and the third chapter was a little less easy, instead of starting like an encyclopaedia, where it's of uniform difficulty and assumes that you know some other stuff. Right at the beginning I tried to make it so you didn't have to know very much and you gradually learned more. I made every chapter so you could read it out loud in an hour, and I felt if you couldn't read it out loud in an hour it was too long. I wanted somebody to be able to sit down and actually read a chapter and not say, "Uh, I give up, I've got half way but I just don't have time to go on", and then maybe never come back. Instead I felt if they got to the end they would feel success, and then on another day they would feel like they should try another chapter, and in that way they got deeper and deeper into the difficulties that we all know about ion channels.

AB: And how did the book evolve over the subsequent editions?

BH: Well, it got longer. The first time I wrote the book there were 7,000 papers about ion channels, the second time there were 30,000, and the third time there were 100,000 papers out there in the literature. For that reason I'm not ever going to do that again (laughs)! The third edition, I feel retrospectively was much too long, it should have been briefer like the original edition, which had the real advantage that you could almost have it as bedtime reading instead of having to labour over it.

AB: Your style of writing has always struck me as a sort of perfect balance of amenable prose combined with scientific insight. Are you a naturally gifted writer or did you actively study how to write accessible scientific prose?

BH: I think scientists are bred to be modest, most of them, so (laughs) it's not appropriate to say that I'm a naturally gifted writer!

AB: Did you study creative writing at university?

BH: Well, yes, in a way. In all the schools that I went to I took courses, which in American education are typically required, on writing essays and writing compositions. I enjoyed it enough that I think I learned a lot from each of the teachers on how to do that. Right from the seventh grade I'd say I learned a lot. I also studied. If you read authors who you think write in a way that's accessible, those are good models for how to write. So if you read William Faulkner and you find it difficult to read, I wouldn't write science like that. If you read Winston Churchill, about the Second World War, it's very accessible and so maybe that's a good way to write. You can look at different authors, completely out of science now, and decide and just say, "Now I'm going to look at the page to see how long the paragraphs are and what they said in the first paragraph and how they developed the paragraph." I don't want to know about this battle in the Second World War, but I want to see how the words were put together in a way that seemed to work.

Readers interested in Bertil Hille's career are directed to an extensive interview conducted by Eric Kandel on the occasion of the Lasker Foundation Basic Medical Research Award to Bertil in 1999[1]. In addition, Bertil has contributed a chapter to *The History of Neuroscience in Autobiography* series published by the Society for Neuroscience, which will be included in Volume 7 to be published in 2011.

[1]http://www.laskerfoundation.org/awards/1999_b_interview_hille.htm

A. V. Hill's photograph album

Hill's papers in the Archives at Churchill College Cambridge are filed in dozens of manila envelopes. Among them is an album of photographs from the 1920s, mostly of fellow scientists. His grandchildren recall that he was a keen photographer with a home darkroom. Some of his photographs are eye-catching. (He was also good at drawing.)

Obviously he did not take Fig. 1, but it may have been taken with his camera. It shows Hill and Otto Meyerhof. They shared the Nobel Prize in 1922 for their discoveries on muscle (Katz, 1978). Hill used thermocouples to measure the heat released during contraction and recovery. Meyerhof measured the rise in lactic acid during tetanus and its fall during recovery, when part was oxidized and the rest rebuilt into carbohydrates. They are at the German border on their way to Stockholm for the Physiological Congress of 1926. Their costumes suggest that they may have been travelling in an open automobile. Hill was keen on cars, motorcycles and power boats.

For the first 16 months of World War I Hill served as an infantry officer. Then he was transferred to the Ministry of Munitions to work on anti-aircraft gunnery, because, as he put it, he "had shown signs of the unpleasant habit of inventing things" (Hill 1918). He devised a method for measuring the position of flying objects with two widely separated mirrors. Conscription forced him to recruit over- or under-age, mathematically talented collaborators. Eventually there were more than 100; they were dubbed "Hill's Brigands". With the mirrors they located shell bursts from test firings. First trained in maths, Hill became known in physiology by fitting equations to data on the contraction of the frog rectus abdominis in response to different concentrations of nicotine, based on nicotine binding to a receptor substance in the muscle, and to

Figure 1. A. V. Hill (1886–1977) is on the left; Otto Meyerhof (1884–1951) is on the right. (All photographs are from the Churchill Archives Centre, A.V. Hill Papers, AVHL II 5/119.)

Figure 2. William Hartree (1870–1943) dissecting a frog muscle in the Cambridge Physiological Laboratory. Note his cylindrical slide rule for high-precision calculations. Some of his maths was to correct their thermocouple measurements for the delays in their recording apparatus.

Figure 3. Ernest Starling (1866–1927) in his laboratory at UCL with two assistants. His gaunt, cachectic appearance shows that his health was failing; in 1920 he had been operated on for a colon cancer.

data on the dissociation of O_2 from haemoglobin, introducing the idea that it has several binding sites. The Brigands pulled off the greater challenge of fitting the positions of shell bursts with equations that accurately describe the path of projectiles hurtling skywards, including the effects of wind, temperature and shell velocity. They also developed apparatus to locate aircraft by sound. The Brigands took their science into the field – they pioneered operations research.

Hill led the group intellectually and also made science glorious fun. One of his recruits was William Hartree (Fig. 2), a retired engineer, who so enjoyed working with Hill that after the war he stayed on as a volunteer. Together they published 36 papers on muscle.

After the war, Hill became professor at Manchester, where he studied human exercise, coining the term 'oxygen debt'. He was a keen runner. Then he was brought to UCL to replace Ernest Starling (Fig. 3), who became a Foulerton Royal Society research professor (Henderson, 2005). Every physiologist can list Starling's great ideas that emerged from brilliant experiments. On a memorable day in 1902 he and his collaborator and brother-in-law, William Bayliss (1860–1924) were working on pancreatic secretion. It was known that injecting dilute HCl into the duodenum stimulated secretion, even when the vagus was cut. Their hypothesis was that the reflex operated through an abdominal nerve network. Therefore they tied off a segment of duodenum and painstakingly severed every nerve running to it. Dilute HCl injected into intact duodenum elicited secretion. So did injection into the isolated, denervated segment. Quick as a flash, Starling announced that there must be a chemical messenger. He snipped out a piece of the isolated segment and ground it in a mortar with sand and some of the HCl. Injecting the filtered solution into the jugular evoked secretion; HCl alone did not. A few weeks later they proposed that such chemical messengers should be called hormones.

Figure 4. Ivan Pavlov (1849–1936).

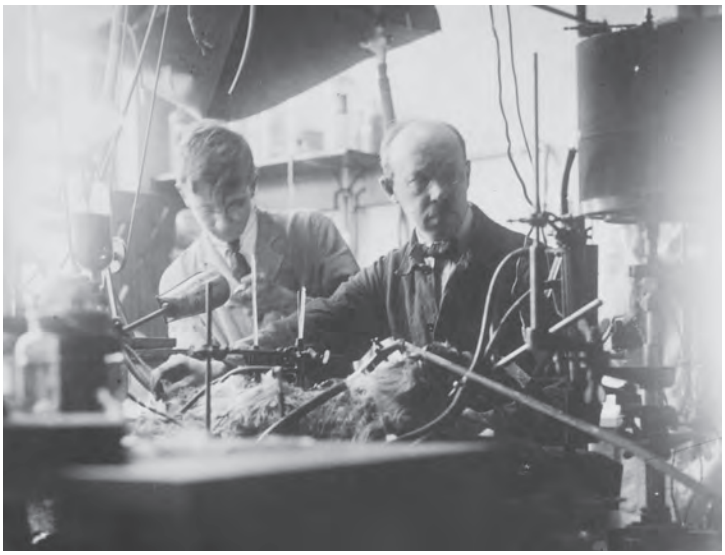

Figure 5. Gleb Anrep (1891–1955) on the right, working at UCL during the 1920s.

The doyen of gastrointestinal physiology was Ivan Pavlov (Fig. 4). He measured the volume and composition of digestive secretions by diverting output to an opening on the dog's body surface; he would study these animals for years. He concluded that these secretions were regulated by nerve reflexes.

In his Nobel Lecture in 1904 he did not mention hormones. He had tried to repeat the UCL experiment, but his intestinal extracts did not evoke secretion. On the other hand, he had reported that stimulating the vagus elicits copious secretion from the pancreas; at UCL vagal stimulation elicited scanty secretion at best.

Pavlov came to England in 1912 for the celebration of the 250th anniversary of the Royal Society, and also received an honorary degree from Cambridge. Instigated by Hill, when Pavlov sat after receiving his diploma the students lowered from the ceiling into his lap a toy dog kitted out with glass and rubber tubing. Pavlov prized this salute from the younger generation and it is now displayed in a St Petersburg museum (Henderson, 2005).

The conflicts in results were resolved in 1912 when Pavlov sent a medical student, Gleb Anrep (Fig. 5), to UCL during the long vacation (Gaddum, 1956). They showed him how to prepare the hormone. They also showed him that Pavlov's protocol destroyed the secretin by over-neutralizing the extract. In his turn, Anrep tried to show them that vagal stimulation elicited pancreatic secretion. His first two tries failed. He discovered that UCL dogs were given morphine before anaesthesia. It was not used in Russia. Without morphine, vagal stimulation worked splendidly. Anrep visited thrice in the next years, publishing his first paper in *The Journal of Physiology*. His last visit was cut short by the outbreak of war in 1914. He returned to finish medical school and then served in the Russian Army and the White Army. When the counterrevolution was defeated he emigrated to Britain, working at UCL and Cambridge. He translated Pavlov's lectures on conditioned reflexes, published in 1927, for which the Royal Society paid him £100.

Anrep's father was a pharmacologist who, at the Tsar's command, established the first medical school for women in Russia. Female physicians were needed because Moslem women would not be treated by males. This may have influenced his son's undertaking a professorship at the University of Cairo in 1931, where he strove to build a department like Pavlov's and Starling's. He worked on histamine and set up the first human heart–lung preparations. He was sacked following the nationalist revolution in 1952.

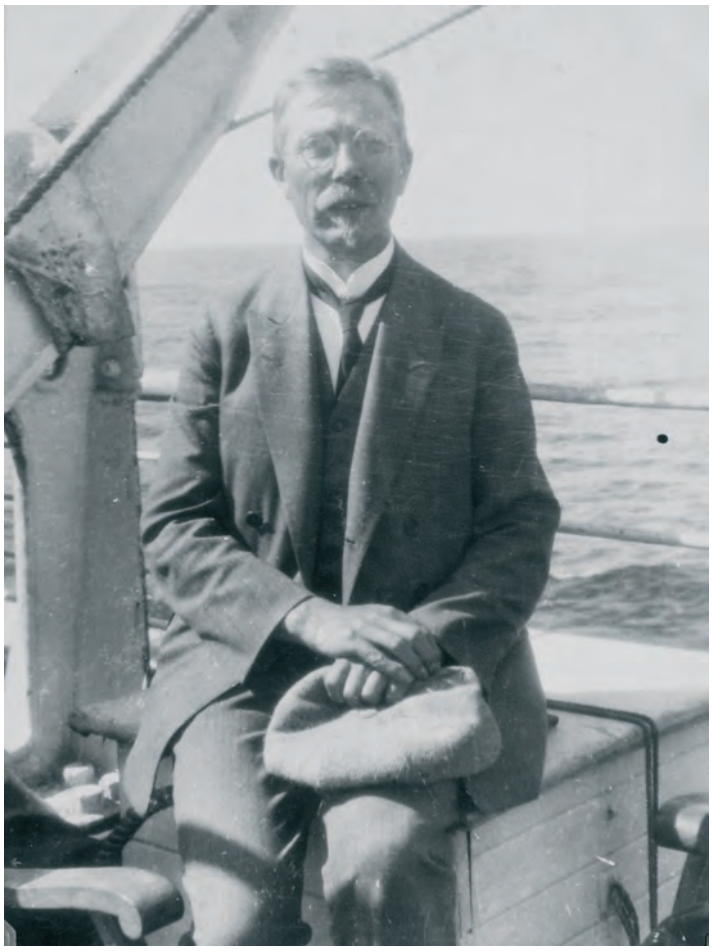

Figure 6. August Krogh (1874–1949).

August Krogh (Fig. 6) shared Hill's interest in exercise physiology (Henriksen, 2000). He was awarded the Nobel Prize in 1920 for proving that capillaries open up when muscles contract, which he showed by injecting India ink into the circulation and then fixing and sectioning resting and contracting muscles. The University of Copenhagen established a Department of Zoophysiology for Krogh and his wife Marie, also a talented experimenter. They showed that oxygen diffuses from the alveolus into the blood. Previously, J. S. Haldane, at Oxford, and J. Barcroft, at Cambridge, had argued that oxygen must be transported actively. At the end of his life Krogh was investigating active transport of ions into marine organisms. He was curious about everything. He worked on topics as diverse as the diet of Eskimos, the physiology of the blue whale, and how insects prepare for flight.

In 1926 Hill also became a Foulerton professor, which freed time for research, but he was not permitted to opt out from UCL committees, where he did such good service. (Starling had been allowed to escape, and was missed.) The wise hand steering the biological side of the Royal Society at that time was William Bate Hardy (Fig. 7). He started as a zoologist, taught histology to the Cambridge physiology students, studied the effects of radiation on cells (burning himself with radium carried in his vest pocket), and then moved on

Figure 7. William Bate Hardy (1864–1933). Labelled in the album as 'W. B. Hardy photographed by A. V. H. at University College.'

to colloids, lubricants, and finally marine biology. If one follows the steps it was a logical progression. As a scientific statesman he was a model for Hill, who in turn became deeply involved in public issues, even serving a term as an MP. Both had to cope with the irrationality of politics. For example, in 1917 Hardy had to cope with a government food controller who instructed the public not to eat bread and meat at the same sitting because it doubled the work of digestion.

Otto Loewi (Fig. 8), professor of Pharmacology in Graz, Austria, took a prominent role in the 1926 Physiology Congress, where he was invited to demonstrate his great experiment – famously its protocol came to him in a dream. He stimulated the frog vagus for a few minutes until the isolated heart slowed and contracted with less force. Then he transferred the Ringer solution from this heart to a second, which also slowed and beat less strongly, showing that the vagus released a chemical. This experiment is tricky to replicate. Usually released acetylcholine is swiftly hydrolyzed by acetylcholine-esterase. He was lucky. His first tries worked because he used winter frogs, some of whom have a low titre of the esterase. Those who tried unsuccessfully to replicate his experiment were naturally dubious. After he identified the transmitter he solved the problem by inhibiting the enzyme with neostigmine, but naturally was apprehensive – we all know that demonstrations are dicey. In Stockholm he was successful 18 times with the same two frog hearts. (Loewi, 1960)

The photograph in Fig. 9 of L. J. Henderson must have been Hill's favourite: there are two different prints in the album. A Harvard professor, it was taken at his camp at Morgan Center Vermont. Every physiologist knows the Henderson–Hasselbalch equation, a product of his work on the physical chemistry of blood. Like Hill he was a champion of biophysics. He was celebrated for his writings on how the earth's chemistry favoured life. He also strongly supported and taught an esoteric theory of sociology.

The Nazis threw out hundreds of intellectuals in the 1930s – an astonishingly generous donation to their opponents. Hill was active in finding places for scientific castaways; for example, bringing Bernard Katz to UCL. Meyerhof ended his career at the University of Pennsylvania and Loewi at NYU. In 1951 they had an embarrassing encounter on a train going from New York City to New Haven, Connecticut. Both were on their way to Yale to receive honorary degrees, but were pledged to

Figure 8. Otto Loewi. He shared the Nobel Prize for 1936 with his friend Sir Henry Dale for their work on chemical transmission. They first met in Starling's lab at UCL in 1902.

Figure 9. Lawrence J. Henderson (1878–1942). Under the second print of this photograph in his album Hill wrote, 'And the spirit of God moved up the face of the waters.'

secrecy, so during the journey they meticulously, but with obvious difficulty, evaded discussion of why they were on the train.

William Van der Kloot

SUNY at Stony Brook

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Acknowledgements

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'...and nothing but the truth'. Simon Singh discusses the peculiar nature of British libel law

I wrote an article in the *Guardian* in April 2008, which criticised spinal manipulation as a treatment for children with asthma, ear infections or colic. The British Chiropractic Association (BCA) was somewhat upset by my analysis of the evidence, but instead of discussing the evidence, the BCA threatened legal action against me personally. The *Guardian* tried to find a compromise, but the BCA refused the offer of a clarification and rejected a right of reply. So, before the summer was over, I was being sued for a libel.

The case lasted two years until the BCA eventually dropped its action against me, thereby allowing my article to go back online and my concerns to be aired once again. As the case progressed, I received a great deal of support from researchers, doctors, journal editors and, in particular, The Physiological Society, who were all outraged that a medical debate was being crushed by a legal threat.

Many words have been written about the reasons why English libel law is so terrible, so I will not bother going through the problems again. However, if you have not followed libel debate, then I would encourage you to read the archive of the legal blogger Jack of Kent (http://jackofkent.blogspot.com), who has covered my case and the campaign for libel reform with clarity and expertise. In the meantime, I will point out that it is easy to see that there must be something wrong with our libel law by looking at how the rest of the world views our approach to free speech.

For example, overseas claimants who try to quash criticism about themselves will try and bring a libel case to London, the world's libel capital, if at all possible. This is not because our libel law is so great, but rather because it is so anti-free speech. We now have the embarrassing situation whereby

Simon Singh

Britain has a growing reputation for libel tourism. In other words, Russian oligarchs, Saudi billionaires and overseas global corporations sue overseas journalists at the Royal Courts of Justice.

The problem is so serious that Americans, who truly value free speech, have made no secret of the fact that they have nothing but contempt for English libel law. Indeed, this year President Obama signed legislation that effectively blocks the impact of English libel law on US citizens.

Despite the growing campaign for libel reform, there are some people who ask if libel is really such a big problem. They may have read about my particular legal battle, but they wonder if one libel case is enough to justify changing the entire law.

Unfortunately, my case is not the only one. During the course of my case, Ben Goldacre and the *Guardian* newspaper were sued for libel for criticising Matthias Rath, who promoted vitamins in South Africa to treat AIDS patients. Rath eventually backed down, but the *Guardian* lost £175,000 in unrecovered legal costs.

And there is the case of Professor Francisco Lacerda of Stockholm University, who criticised a supposed lie detection device in an academic journal. The Israeli technology company behind the device sued for the libel and the journal could not afford to defend itself, so Lacerda's article was withdrawn. The UK government has spent £2m on the device, but we can no longer read Professor Lacerda's critique.

Another case involved the Danish radiologist Henrik Thomsen, who was sued in London by America's GE Healthcare Corporation for slides presented at an academic seminar in Oxford. For over two years he came under intense legal pressure to apologise for raising concerns about Omniscan, a contrast agent used in patients undergoing MRI scans. Eventually, public outcry and the lack of any real case caused GE Healthcare to drop the case.

The eminent English cardiologist Peter Wilmshurst is currently being sued in London by an American company after comments made in America at an American conference to an American online magazine. After almost three years of refusing to back down on a matter of public interest, Dr Wilmshurst risks bankruptcy if the judge ultimately rules against him.

Most bizarrely of all, the journal *Nature* is in the middle of a libel battle after being sued by a cosmologist.

These cases are merely the tip of the iceberg. Many other libel actions are settled at an early stage, when authors and publishers who cannot afford the risk of losing will back down and apologise even if they believe their criticisms are valid.

And there are countless authors who self-censor articles, books and papers because of the co-called chilling effect of libel. We rarely appreciate the extent of this problem, because the damage is done prior to publication, but I was made very aware of it when

Nick Miller, health correspondent at the Australian *Age* newspaper, interviewed me about homeopathy. He wrote up the interview, but his in-house lawyer refused to allow him to quote my harshest criticisms in case the newspaper was sued in London. Instead, he wrote a blog about how tough it was to be a health journalist in Melbourne when there was the threat of ending up in an English court on the other side of the planet. (For the record, I know that all my comments about homeopathy were justified.)

In short, English libel law is relentlessly hostile to writers and scientists, while it seems to be deeply supportive of anyone or any corporation that receives the slightest criticism. The result is that scientific debate is hindered and robust criticism is gagged.

The good news is that Parliament seems to be enthusiastic about libel reform. Indeed, both the previous Labour Government and the new Coalition Government is committed to a Defamation Bill that will be developed over the next year. The Physiological Society and the scientific community in general can take great pride for having helped politicians realise that English libel law is a disgrace that crushes free speech globally.

However, it is still crucial that we continue to speak out on behalf of science and free speech, otherwise vested interests will pressurise politicians into creating a watered down and ineffective libel reform bill. If you have not yet signed the petition for libel reform, then please visit www.libelreform.org – and if you have already signed, then please encourage friends, family and colleagues to back the campaign for libel reform.

Simon Singh

Simon Singh is a science writer and the author of *Fermat's Last Theorem*, *Big Bang* and *Trick or Treatment? Alternative Medicine on Trial* (with Professor Edzard Ernst).

The other brain: from dementia to schizophrenia, how new discoveries about the brain are revolutionizing medicine and science

By R. Douglas Fields
Simon & Schuster
£17, 384 pages, hardback
ISBN-10: 0743291417
ISBN-13: 9780743291415

For too long neuroscientists have neglected glia in favour of their more electrically excitable cousins, the neurones. Only with the advent of calcium imaging and a variety of other modern techniques, have glia revealed their secrets, which long remained hidden in times when electrophysiological recordings were the dominant tools of neuroscience. Inspired by his own research into the subject R. Douglas Fields dedicates the majority of just over 300 pages to carefully explaining why glial cells, 'the other brain', demand our collective attention.

The book is aimed at a general audience, and Fields does an excellent job of explaining introductory concepts for glia novices. The structure of the book is thoughtful and fluid. In three acts we are included in Fields' exploration of the annals of the history of glia. He starts with Marion Diamond and her endeavour to unlock the mysteries of Einstein's brain and the key to his genius (the answer is astrocyte density), then an intermission to cover neuroscience essentials. The main text of the book is then taken up with Fields' exploration of the involvement of glia in health and disease starting with the long-established roles in brain cancer, infection and injury to more nebulous failures of the brain such as psychiatric illness, neurodegenerative disease, pain and ageing with a final section on glia in thought and memory and the unconscious mind. Individual chapters are devoted to each topic and can be read as self-contained treatises. It is within these chapters that the true contribution of glia to brain function and dysfunction is revealed.

It is the encounters with great minds, the brilliant and sometimes vivacious characters behind the major advances in the study of glia where the narrative really shines. Palpable glee and insights into vivid imaginations make these additions a real joy. Fields explores the contributions of a number of scientists: from the foundations of modern neuroscience with Ramon Y Cajal, Golgi and his student, the Arctic explorer and part-time neuroscientist Fridtjof Nansen, who touted glia as a possible 'seat of intelligence', through to Rudolf Virchow's notorious coining of the phrase that translates to 'neuro glue', to the bolshie and determined American physician Gajdusek who muscled less able and resolute researchers out of the way to elucidate the secrets of the devastating disease Kuru. The sad fate that befell Schwann at the hands of his fellow academics is a sanguine warning of the consequences of unjustified criticism.

Fields is clearly baffled at how these cells could have been overlooked and neglected for centuries. He concludes that research in this 'other brain' is over a hundred years behind that of the neuronal brain and believes that this is why much of the functioning of the brain eludes our grasp of understanding. Overall the narrative is engaging and accessible and it fills a noticeable gap as a highly recommended complementary text to undergraduate studies.

Angus Brown and Julia Barber

Life Science Careers Conference 2010

The next conference, for undergraduates and postgraduates working in the life sciences, will be held at King's College London on 24 November 2010. Registration is now open.

The conferences cover a wide range of science-related career opportunities, a CV workshop providing tips on how to ensure you secure an interview, and a chance to mingle with experts and ask informal questions.

Registration is £10 and includes entry to the exhibition hall, lectures, a buffet lunch and refreshments.

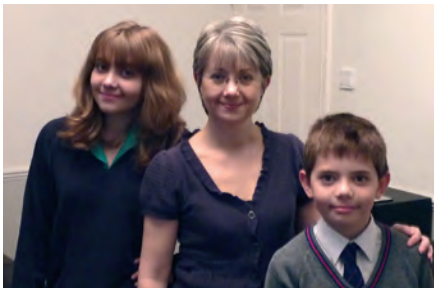
Inspiring women – The Society mentoring scheme

The Physiological Society's mentoring scheme for women is entering its second year with over 50 participants already. In 2009, 10 mentees were matched with 9 mentors, and this year the numbers have increased with 16 mentees matched with 15 mentors. This scheme is aimed at helping women progress and stay in science by allocating women a mentor to discuss issues and problems that may arise. Despite improvements in government policy and even support by the Prime Minister to try and improve the gender balance in science, engineering and technology (www.theukrc.org/news/2010/07/ukrc-addresses-pm-on-his-policies-for-supporting-women), there are still fewer women continuing a science career.

In the next few issues of *Physiology News* we are hoping to help to inspire young scientists by interviewing women that have been very successful in their careers.

This first article looks at balancing a family and other parts of your life with a science career. In a recent report married mothers are 35% less likely to enter tenured posts than married fathers (*Nature* **462**, 375, 18 November 2009). Furthermore, mothers who do try and continue science careers tend to devote most of their non-childcare time to their career (*Nature* **466**, 279, 7 July 2010).

I am a mother with three young children who strives to get the life–work balance and I try to ensure that I devote enough time to the family as well as progressing through on my career (I am currently an ESRC Research Fellow but have a permanent position as a Senior Lecturer at the University of Essex). I am always inspired by women who are managing to keep not just their careers going but also manage a hectic family life too. One such inspiring person, whom I met on my time on The Physiological Society Council, is the Head of the Education Committee Louise Robson. Recently I met up with Louise and posed her a few questions to find out what drives her, who inspires her, what she does in her spare time (if she has any) and what her personal goals are.



Louise Robson and her children.

Valerie Gladwell (VG): Who are you? Tell us a bit about you and your family.

Louise Robson (LR): I am married to Richard (just celebrated our 20th wedding anniversary) and have two kids – Jacqueline (15) and Oswald (10). I have been in academia for 21 years (from the start of my PhD).

VG: Where do you work?

LR: I work at Sheffield in the Department of Biomedical Science, and have been here for 14 years. This was my first academic position, and I started as a junior lecturer, before promotion to senior lecturer a few years ago.

VG: When did you start your career in science and can you tell us about your key milestones?

LR: I started 'work' in science at the start of my PhD in 1989. Key milestones for me would be: (1) Doing a summer vacation project as this was the reason I decided to do a PhD. (2) Winning the scholarship that allowed me to do my PhD. (3) Getting my academic position at Sheffield. (4) Winning the first ever Biller prize. (5) Publishing my first independent paper. (6) Taking over as chair of the Education Committee at The Society. (7) Winning a Senate Award for sustained excellence in learning and teaching at Sheffield.

VG: Why a career in science?

LR: I always enjoyed science at school and for me I knew I wanted a career involving bioscience. I actually had a place to study medicine, but dropped a grade in my physics A level and ended up doing Physiology at Leeds (got in through clearing). This was actually the best thing that happened as I quickly realised I loved the basic science side of human biology, particularly physiology (I also had to do Pharmacology and Biochemistry in my first year). When I completed two lab projects during my degree (a summer vacation one, funded if I remember correctly by The Society and a final year project) I knew that a PhD and research was for me. I really enjoyed the challenge of learning new techniques, getting to grips with designing experiments to address research questions and then presenting my findings in the context of the literature. Funnily enough I also ended up doing some teaching during my PhD, and from then on I was hooked on getting an academic position.

VG: Is there any moment you can remember that stands out which changed your career path?

LR: The biggest moment was winning my scholarship, as without this I would not have been able to do my PhD and I probably wouldn't be doing my job (which I love).

VG: Who inspired you?

LR: It has to be my PhD supervisor, Malcolm Hunter, who has just retired from Leeds. He was amazing! He instilled in me a passion for both research and teaching, something that I still have today. The dedication he showed to both these areas made a massive impact on my own work ethic.

VG: What is your current role at work?

LR: I am a senior lecturer and also chief UCAS selector.

VG: Briefly what does this involve?

LR: You name it I do it! I have a research lab, with a postdoctoral researcher, technician and two PhD students. I have a heavy teaching load as I teach across all levels, particularly final year students. I run undergraduate admissions for the department. I also run our summer vacation studentship scheme (to try and get the current students into research and academia). I am also chair of the Education Committee at The Society, and Member of Council and Exec.

VG: What is your current research area? How much time do you get to devote to this?

LR: I am interested in ion channels in epithelial cells, particularly in the kidney and the airway. I am currently working on K^+ (renal) and Cl^- (airway) channels. I spend about half my time on research, although I don't get to spend as much time actually doing the research as I would like.

VG: Can you give us one of your key papers?

LR: One of the first papers I published as a principal investigator: Na^+–alanine uptake activates a Cl^- conductance in frog renal proximal tubule cells via nonconventional PKC (2001). ID Millar and L Robson. *Am J Physiol Renal Physiol* **280**, 758–767.

The first paper from an ongoing collaboration:

The formation of the cAMP/protein kinase A-dependent annexin 2–S100A10 complex with cystic fibrosis conductance regulator protein (CFTR) regulates CFTR channel function (2007). LA Borthwick, J Mcgaw, G Conner, CJ Taylor, V Gerke, A Mehta, L Robson and R Muimo. *Mol Biol Cell* **18**, 3388–3397.

VG: What are your career goals? (Where would you like to see yourself in 10 years?)

LR: I absolutely love my job, and wouldn't want to do anything else, although I am looking towards promotion to professor. I know that some senior academics take a large management role as they progress through their careers, but I am not sure that is for me. I enjoy my research and teaching too much!

VG: What have been your barriers/hurdles to overcome to get where you are now?

LR: My biggest barrier was not being eased into teaching when I started at Sheffield. As I was recruited to start teaching straight away, I took on a full teaching load from the word go. This meant that I had less time for research in the first few years compared to others, and I know this has impacted on the development of my research lab. As a female I cannot say any of the typical perceived barriers have impacted negatively. I have a family, and had my first child when a postdoc and then my second as a lecturer. For both I took 7 months 'off', although I did do some work during that time

Valerie Gladwell with her family.

to keep in touch. Coming back and juggling family life and work demands was difficult. So perhaps the best piece of advice I would give would be to make sure you are completely organised in all aspects of your life – it makes it much easier to achieve in all areas.

VG: You are part of The Physoc Council; how did you get involved? What is your role?

LR: I joined Council when I was asked to take over as chair of the Education Committee. This role involves overseeing all of the educational activities of The Society. It is quite a big job, but helped out by the great staff we have in The Society office and Members of the Committee as well. Given that our activities cover the full spectrum from schools to postgraduate/postdoctoral support, the committee has a huge variety of schemes to run and evaluate. Of course, we are always looking for new ways to improve our educational impact as well. As chair I also sit on the Executive Committee and therefore play an important role in taking suggestions and ideas to the other trustees to ensure that The Society is doing the very best for its Members.

VG: What do you think could be done to improve retaining women in science?

LR: I received great support from my bosses when pregnant and then on maternity leave, but I know that not all women get the same treatment. So one thing that needs to change is the attitude to women taking time off to have a family. How to achieve this is another question, and one that I am not sure I can answer. One thing we can do is let young female researchers know that success can be theirs. The Society is doing this in a number of different ways. For example, we are running a mentoring scheme, pairing junior female researchers with experienced female academics. The Society has also recently become involved with the Daphne Jackson Trust, part sponsoring a scholarship for a female physiologist to go back into research after taking a career break.

VG: Is there any aspect of life you would like to improve on?

LR: I would like to spend less time at my desk pushing pieces of paper around and have some time to get into the lab.

VG: How would you like to be remembered?

LR: As someone who always put 100% into everything they did.

VG: Spare time! Do you have any? What do you do?

LR: I like to think I have a good work/life balance. Both of my children are competitive swimmers, so my husband and I spend quite a lot of time at swimming pools so they can train or race. The club they belong to (like most kids sports clubs) is run on a voluntary basis, and we help out as much as possible. I sort out the gala entries, run the web page and actually teach little ones to swim as well. I recently passed my level 1 swimming teacher qualification and have also recently passed level 2 (it was somewhat scary doing exams again after so long). This means I am really busy, but I find the different activities I do at the club really keep me motivated at work.

VG: You sound like you are a super hero but if you could be any superhero what would you be?

LR: Supergirl, so that I could fly to work and not have to use public transport to commute every day! This would give me more time at work.

Exercise can help rewire the brain: neuroplasticity and motor cortex function in physically active individuals

Recent evidence with magnetic brain stimulation in human subjects shows that participation in regular physical activity influences brain function by enhancing neuroplasticity in motor cortex, which could improve motor skill learning and neurorehabilitation in physically active individuals.

Regular exercise is known to have an impact on most physiological systems, and has been shown to improve cardiovascular health, bone mineral density, and provide a decreased risk for cancer, stroke and diabetes. More recently, epidemiological evidence has accumulated to suggest that physical activity may provide health-protective benefits for the nervous system, including improvements in several neurological diseases. In addition to these neuroprotective effects, exciting new evidence has emerged indicating that regular physical activity and exercise can increase brain plasticity (i.e. the capacity to reorganize connections in the brain), which is a process believed to be instrumental in the formation of memories and learning. These neuroplastic benefits of exercise are not only important for cognitive function, but may also extend to the neuromotor system to facilitate motor skill learning.

In humans, robust effects of exercise have been most clearly demonstrated in ageing populations during tasks that specifically assess neurocognitive function (Colcombe & Kramer, 2003). These effects have been neatly summarized in a meta-analysis of 18 intervention studies examining the effect of long-term aerobic fitness training on various measures of cognitive performance (Fig. 1). The outcome of this analysis clearly shows that participation in regular physical activity and exercise improves cognitive function in sedentary older adults, with the greatest improvement observed in complex executive-control processes involving coordination, planning and working memory. Furthermore, functional magnetic resonance imaging revealed that highly fit subjects show greater task-dependent modulation of activity in various cortical regions

John Semmler (left) and John Cirillo.

during attention-demanding tasks compared with untrained control subjects (Colcombe *et al*. 2004). These studies suggest that regular exercise provides neuroplastic benefits to the ageing brain, and may even slow the neural ageing process in humans.

While the majority of these studies have focused on plasticity associated with neurocognitive function, it is unknown whether regular exercise is beneficial for neuroplasticity within the motor cortex, which is vital for learning new motor skills. Recent advances in techniques of transcranial magnetic stimulation (TMS) have allowed us to address this question in humans (Cirillo *et al*. 2009). TMS is a non-invasive technique that gives an indirect assessment of motor cortex activity, and offers significant advantages in temporal resolution over other functional imaging techniques. TMS activates excitatory (and inhibitory) interneurons in the cortex, producing descending volleys in corticospinal neurons with projections to spinal motoneurons. This results in a short-latency contraction of contralateral muscles, with the amplitude of the muscle-evoked potential (MEP) from the electromyogram (Fig. 2A) reflecting the excitability of the neurons responsible for the movement of that particular muscle. At the motor systems level, plasticity is examined by using TMS to measure the change in excitability of motor cortex neurons before and after an intervention. Any long-lasting (<1 hour) increase in motor cortex excitability is interpreted as a change in one or more mechanisms responsible for neuroplasticity, with long-term potentiation (LTP) thought to play a major role.

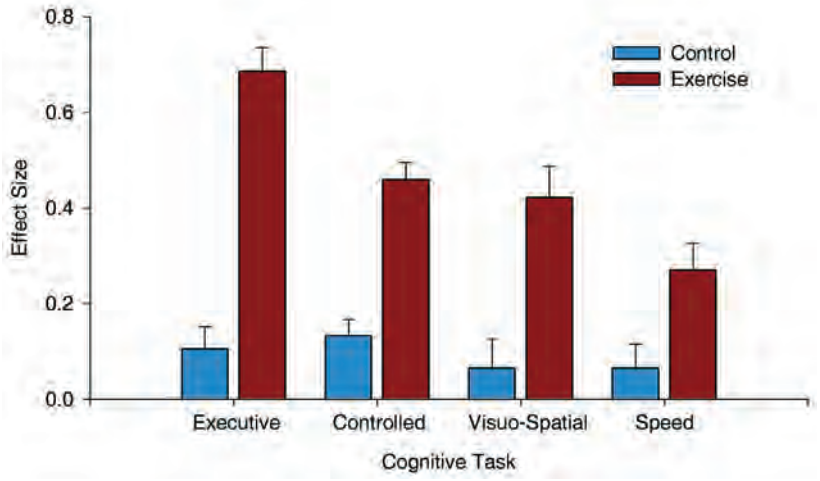


Figure 1. Effect sizes from 18 interventional studies published between 1966 and 2001. Executive tasks rely on complex cognitive function such as planning, inhibition and scheduling of mental procedures. Controlled tasks involve effortful processing such as a choice reaction time task. Visuospatial tasks assess the participants' ability to transform or remember visual and spatial information. Speed tasks involve simple reaction time or finger tapping. Error bars show standard error of the mean. Data were redrawn from Colcombe & Kramer, 2003.

Several experimental protocols have been devised for inducing cortical plasticity in humans (see Ziemann *et al*. 2008 for review). One commonly used protocol to artificially induce changes in the human motor cortex is paired associative stimulation (PAS), which has been deliberately adapted from similar protocols in brain slices and neuronal cultures that demonstrate spike timing-dependent synaptic plasticity. The conventional PAS approach in humans combines low-frequency, percutaneous electrical stimulation of the median nerve at the wrist with TMS over the contralateral motor cortex. The TMS is timed to coincide with the arrival at the cortex of the afferent volley evoked 25 ms earlier by the peripheral stimulus. This protocol results in substantial increases in the amplitude of hand muscle MEPs, which are long lasting (30–60 min), and are thought largely to occur through LTP-like mechanisms in cortical circuits (Stefan *et al*. 2000). Recent studies show that the effects of PAS and motor skill training interact, suggesting that they involve overlapping changes in functionally relevant neuronal circuits.

In a recent study, we used PAS to examine the capacity for motor cortex plasticity in a group of 14 highly active and 14 sedentary young subjects (Cirillo *et al*. 2009). Based on aerobic physical activity assessed via questionnaire, individuals in the active group performed moderate or vigorous-intensity exercise (involving running or cycling) an average of 9 times per week for at least 60 min in each session. In contrast, individuals in the sedentary group performed no more than three sessions of walking each week for 20 min each session. All other characteristics were well matched between groups, such as age, sex, handedness and cognitive state. Using TMS, we found that the input–output curve for a small hand muscle was steeper in active subjects (Fig. 2B), suggesting increased excitability in the corticospinal pathway to muscles not directly involved in the exercise. Furthermore, we found a 40% larger MEP in the active compared with the sedentary subjects after PAS (Fig. 2C), suggesting that regular physical activity involving aerobic exercise contributes to increased neuroplasticity after PAS. These findings indicate that regular exercise may offer benefits to motor cortex function that extend beyond the neural boundaries for control of the exercising limb. Although many mechanisms are possible, the beneficial effects of exercise on brain plasticity are likely to be mediated by increased vasculature, blood flow or growth factors that provide a more supportive cortical environment.

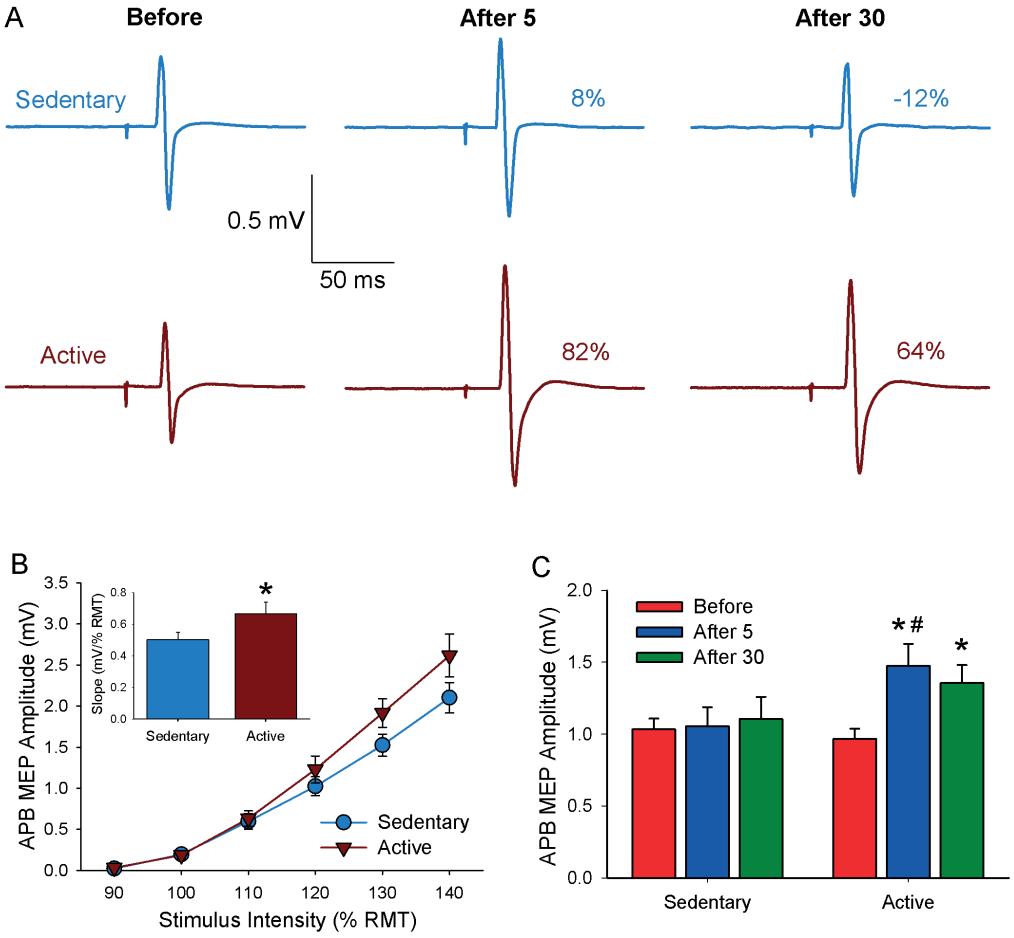


Figure 2. A, averaged MEPs (n = 10) in the abductor pollicis brevis (APB) muscle obtained before and after PAS. The numbers indicate the percentage increase in MEP amplitude after PAS. B, TMS input–output curve in 14 sedentary and 14 active subjects. C, mean (± S.E.M.) MEP values obtained in 14 sedentary and 14 active subjects before, 5 min after (After 5) and 30 min after PAS (After 30). RMT, resting motor threshold. Data were obtained from Cirillo *et al*. (2009).

An important extension of this work is determining whether these differences in neuroplasticity are functionally important for learning new motor skills. As a first step in addressing this question, we have obtained preliminary data on motor performance and motor cortex plasticity in two sedentary and two active subjects that took part in our original investigation. The task was a brisk thumb movement to maximise acceleration in the abduction direction. These data show improved motor performance and faster learning in the physically active subjects, particularly in the early stages of training (Fig. 3). Furthermore, increased MEP amplitudes and TMS input–output curves in physically active individuals accompanied this improved learning after training. These preliminary data suggest that there is increased motor cortex plasticity in physically active individuals, and that this is accompanied by improved ability to learn new motor skills. However, we cannot yet exclude the possibility that the increased plasticity in physically active individuals is influenced by genetic or epigenetic factors, which makes these individuals more likely to participate in regular physical activity. Nonetheless, these findings offer promising new insights into the benefits of regular exercise on the motor system, which may improve motor skill learning and neurorehabilitation in physically active individuals.

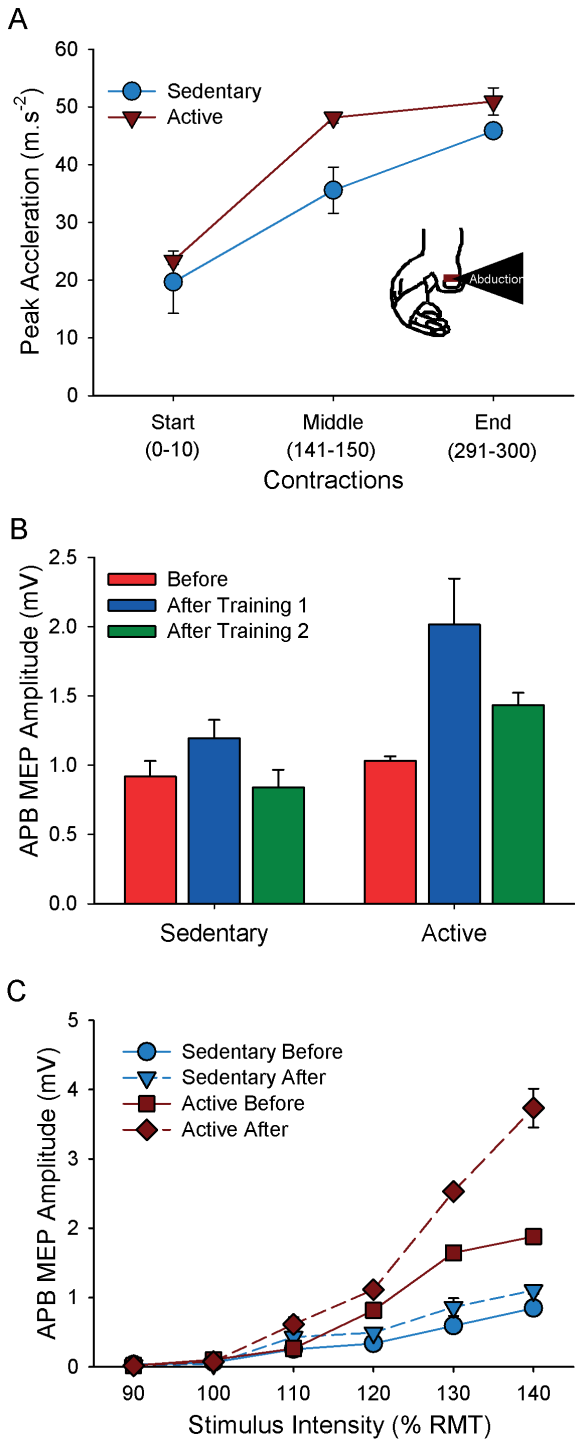


Figure 3. A, mean peak thumb acceleration with brisk thumb training in 2 active and 2 sedentary subjects obtained at the start (1–10 movements), middle (141–150 movements), and end (291–300 movements) of training. B, mean APB MEP amplitudes obtained before, immediately after (Training 1) and ~25 min later (Training 2). C, TMS input–output curve before and after training in sedentary and active individuals.

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Acknowledgements

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The physiology of *Casino Royale*: proteins to parkour

In the film *Casino Royale*, James Bond chases terrorist Mollaka over a construction site in Madagascar. Mollaka leaps from crane to rooftop and from rooftop to ground, landing under control and able to resume running immediately. These stunts are not just filmic tricks – Mollaka (Sébastien Foucan) is a top class exponent of free running or parkour (see www.youtube.com/watch?v=Q0e7akuSgKI). Despite Foucan's skill the shock to the legs is still enormous – 17 body weights for a 1.8 metre fall (Yeadon *et al*. 2010). How can he absorb this shock without injury? In engineering, shock absorbers prevent high-impact forces by creating constant deceleration over a given distance or stroke length. Springs produce high decelerations towards the end of the impact and dashpots produce high decelerations at the start, thus many industrial shock absorbers use a combination of the two.

So where are the springs and dashpots of human shock absorbers and how do they work? To answer this we need to integrate research findings all the way from the molecular mechanisms of muscle cells to the neural control of falling and landing.

On landing the impact causes ankle, knee and hip joints to rotate. This stretches the muscles opposing the movement which lengthen under control, reducing joint rotations and acting as a brake. When muscles are braking and lengthening the relationship between force and velocity is quite different from A.V. Hill's classic shortening force–velocity curve. Firstly, force increases with velocity (dashpot effect); secondly, force increases with the amplitude of stretch (spring effect); and thirdly, the force can be up to twice that produced by an isometric contraction. Figure 1 shows the combined effects of amplitude and velocity for a human muscle. These properties make stretching muscle a particularly effective brake; the greater the shock the greater the force response. So what are the mechanisms of these properties at the molecular level?

Muscle force increases with the *velocity* because stretch causes high positive strain in muscle cross-bridges. This slows their power stroke leaving more and more pre-stroke bridges attached, as velocity increases (Pinniger *et al*. 2006*a*). Force increases with stretch *amplitude* because stretch increases the strain in the elastic crossbridges considerably above the values found in an isometric contraction. The force rises in proportion to the strain until bridge detachment limits the maximum force to around twice the isometric value. Furthermore, recent work has also suggested that greater stretch favours the attachment of the second myosin head found on all muscle crossbridges (Brunello *et al*. 2007) thus increasing the available force. Elastic proteins such as titin within the sarcomere and transverse elastic connections between myofibrils may also increase force when stretched (Pinniger *et al*. 2006*b*).

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Muscle fibres, although beautifully evolved to act as brakes, do not act alone. The shock of landing is also absorbed by the tendons to which the muscles are attached. Tendons have a complex structure but are mainly composed of the elastic protein collagen. They have 70 times the Young's Modulus of fully activated muscle, but their stiffness relative to muscle is reduced because their cross-sectional area is often 30–100 times smaller than the attached muscle. With lower stiffness the tendon can provide a greater proportion of the total lengthening of the muscle–tendon complex. Millimetres of the tendon lengthening will be particularly large when the

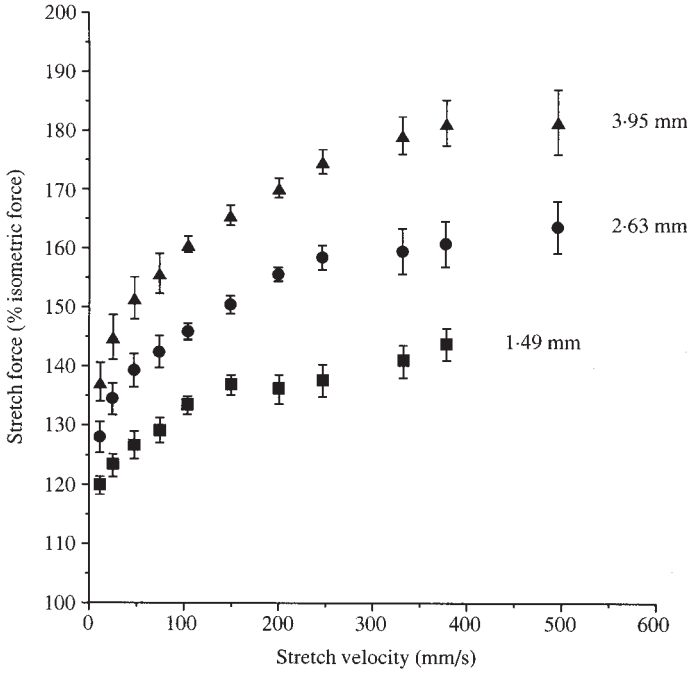

Figure 1. Force–velocity relationship of muscle during stretch. Note how force increases both with velocity and amplitude of stretch. Shortening would show opposite velocity effects and no amplitude dependence. The data are from the first dorsal interosseus muscle of the human hand and include tendon effects (see text). Tendon effects reduce the imposed amplitude and velocity 'seen' by the muscle. Group data from Cook & McDonagh (1995).

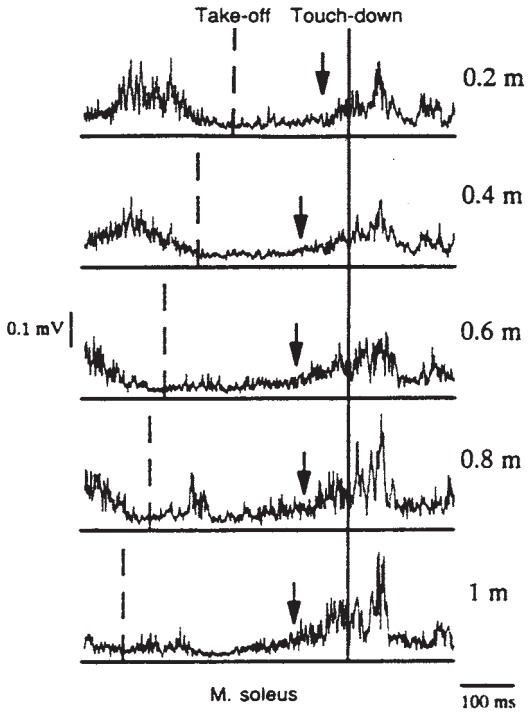

Figure 2. Effect of fall height on timing and amplitude of muscle activation. Fall heights increase from top to bottom. The dashed line marks take off and the arrow marks the start of the activation build-up (using an objective criterion). Note time between dashed line and arrow (latency) increases with fall height but time between arrows to touch-down (duration) is relatively constant. Note greater amplitude and steeper rise of EMG for greater heights. Single subject data for the ankle plantar flexor m. soleus. In later experiments similar results were obtained from ankle plantar flexor m. gastrocnemius and knee extensor m. rectus femoris. From Santello & McDonagh (1998).

tendon is long and thin and the muscle short and fat. For example, it can be calculated from known values of Achilles tendon stiffness and peak impact forces that this tendon could stretch by 13 mm or 16% following a fall from 0.8 m. Tendon stretch has the advantage of both increasing the absorption of energy and preventing over-lengthening and damage to muscle fibres (Cook & McDonagh, 1995).

The energy of impact must be dissipated as well as absorbed, otherwise on landing the subject will be thrown upwards again by elastic recoil. Energy is dissipated as heat by the muscle component which acts as a damper as well as a spring. Damping occurs when impact forces cause actin and myosin filaments to slide apart, detaching crossbridges as they go. In summary, the muscle–tendon complexes of the body are a multi-mass, damped-spring suspension system.

The absorption and dissipation of energy is sufficient to brake a fall because all the joints of the leg are involved. The sum of their rotation amplitudes (e.g. 33 deg ankle, 66 deg knee, 54 deg hip for a 1 m fall) determines the distance the centre of gravity of the body moves following impact. This is equivalent to the stroke length of a mechanical shock absorber. In simple terms $F = m\,g\,h/\Delta h$, with gravitational acceleration (g), the longer the stroke length (Δh), the smaller the average force (F) experienced over the stroke length by the centre of gravity of the subject's mass (m) and the smoother the landing from height (h) (Minetti *et al*. 1998). Joint rotations and centre of gravity excursions increase with higher falls (Santello *et al*. 2001). In parkour the impact force is further reduced by a roll on landing which increases the distance and surface area over which the shock is absorbed. Compression shock to bones on impact is also minimized by landing with slightly flexed joints which rapidly rotate. In addition, co-contraction of the flexors ensures correct stiffness of the extensor muscle brakes combined with the appropriate joint angle prior to impact (Yeadon, 2010)

Muscle–tendon complexes are more than just passive suspension systems, as their damping and the spring constants can be modulated by varying the activation of the muscle component. This is an active suspension system, exactly the type of suspension banned by Formula 1! With too little activation the joints over rotate and the subject collapses in a heap and cannot continue running. With too much activation muscles are stiff and the subject lands like a steel pin, joints under rotate, impact forces are high and bones may be broken. How does the brain get the activation right?

To tackle this question we varied the impact force by asking subjects to fall from different heights whilst we recorded muscle activations from several flexor and extensor muscles of the leg (Santello *et al*. 2001). Figure 2 shows the results. The further the subjects fell the greater the activation of the muscles during the flight. Thus, the central nervous system (CNS) predicts the required activation for each height rather than setting one activation level for all heights. The brain also needs to predict the timing of the impact. A simple strategy would be to contract all the muscles at the same delay after take-off. Is this what happens? No, as Fig. 2 shows, the longer the fall, the longer the brain waits before triggering the contraction. However, the duration of the next time period, from the start of muscle activation to floor contact, is relatively constant, irrespective of fall height. This period also shows how the motor programme increases force. As greater fall heights are perceived, activation rises more steeply so matching muscle force to the expected impact. In summary, the brain appears to predict both the force and timing of impact and to pre-programme the muscle activation required to deal with it. The mechanisms behind these predictions require much further investigation but probably involve a combination of visual distance estimation, mental clocks and sensorimotor memories.

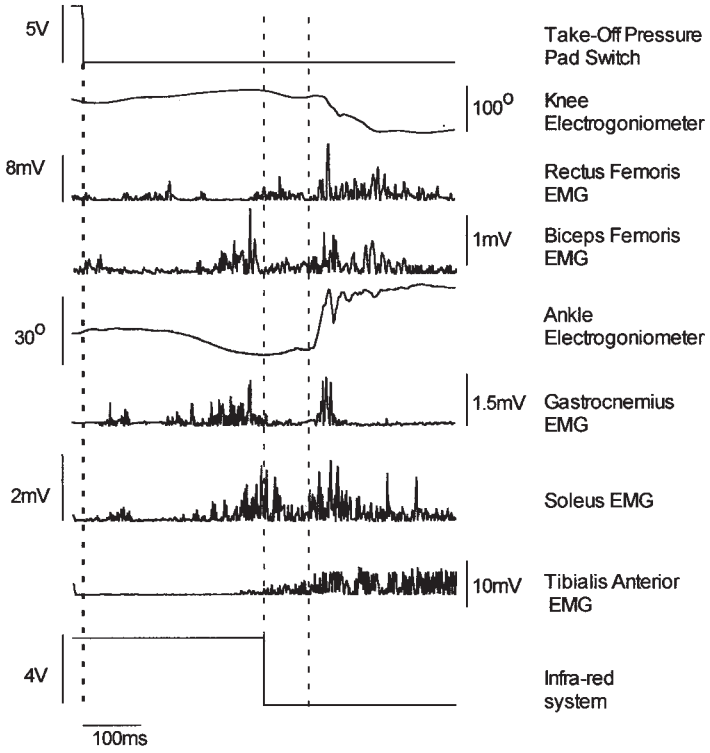

Figure 3. False floor separates pre-programmed and reflex responses. Fall of 0.7 m with false floor at 0.45 m. The three vertical dashed lines mark, from left to right: take off, false floor, and hard floor. Passage through the false floor is recorded by an infra-red sensor. Taking gastrocnemius as an example, note build-up of activation in preparation for false floor, dying away of activity and then reflex at hard floor impact. Single subject data from McDonagh & Duncan (2002).

However, prediction is not the whole story. An examination of Fig. 2 shows that EMG activity continues beyond impact. Is this a continuation of the pre-programmed activation or a reflex triggered by the impact? To settle this question we tricked the brain into expecting a landing after a short fall (0.45 m) but actually provided a lower landing surface at 0.7 m (Duncan & McDonagh, 2000). Subjects expected to land on a false floor which they saw 0.45 m below the take-off platform. This floor easily gave way on contact with joint rotation and muscle stretch only occurring when the subject hit the hard floor a further 0.25 m below. Falls to visible hard floors at 0.45 m and 0.7 m provided controls. The results were clear. The reflex was only present if joints rotated. Figure 3 shows how the false floor trials separated the pre-programmed from the reflex components. This is particularly obvious for the gastrocnemius muscle. Muscle activation whilst airborne was clearly timed to the impact with the false floor. This activation then died away as the subject descended below the false floor to impact on the hard floor. On impact, joints rotated and a reflex response occurred at a mean latency of 56 ms. Thus, the control of landing depends on both pre-programmed and stretch reflex responses.

Our data had one further surprise in store. The amplitude of the reflex at hard floor impact in the 'via false floor' trials was double that for the direct fall (McDonagh & Duncan, 2002). However, joint rotations at impact were the same in each condition and there was no joint rotation at false floor level. Thus, there was a larger response for the same stimulus i.e. an increase in gain of the reflex loop. Eventually we concluded that this increase in gain was triggered by the *non-occurrence* of expected joint rotation at the predicted time of impact i.e. at the false floor. In other words, the *absence* of an *expected* event is as much a signal for the CNS as the *presence* of an *unexpected* one. This idea is probably widely true in many other CNS control systems and deserves much further investigation.

We can now answer, in a nutshell, the '*Casino Royale*' question. Sébastien Foucan can absorb the shock of parkour because muscle–tendon complexes have evolved many ingenious shock-absorbing proteins, and mechanisms. The brain then tunes these shock absorbers using both pre-programmed control and adjustable reflexes to achieve injury-free landings over a wide range of impact conditions.

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Vagal baroreflexes in astronauts during spaceflight

Astronauts returning to Earth from space commonly experience orthostatic symptoms, and rarely, frank syncope. Since a terrestrial analogue of space exposure, prolonged head-down bed rest, impairs both orthostatic tolerance and vagal baroreflex function, we studied the effects of spaceflight on astronauts' vagal baroreflexes. We document significant vagal baroreflex impairment in space, which, considered with earlier studies, indicates that exposure to weightlessness diminishes vagal and augments sympathetic cardiovascular influences.

Before the manned space era, scientists expressed trepidation regarding the potentially baleful consequences of human exposure to the totally unknown physiological influences of microgravity. On April 12, 1961, the Soviets launched the first human into space, Yuri Gargarin. He returned to Earth after an 89 min orbital spaceflight with no apparent disability. However, the ninth man in space, the American Wally Schirra, returned after 9 h and 13 min in space and experienced dizziness upon standing up.

Orthostatic symptoms are common in astronauts returning from space; indeed, Buckey *et al.* (1996) reported that 9 of 14 astronauts could not stand quietly for 10 min, and two of the others felt lightheaded at the end of 10 min. Since a terrestrial analogue of microgravity, prolonged head-down bed rest, provokes both orthostatic hypotension and vagal baroreflex impairment (Convertino

Dwain Eckberg

et al. 1990), it seemed reasonable to test the hypothesis that microgravity exposure impairs human baroreflex responsiveness.

To study this possibility, we modified a neck chamber device (Eckberg & Fritsch, 1993), described originally by British Royal Air Force Flight Lieutenants, J Ernsting and DJ Parry (1957), to elicit entire sigmoidal baroreceptor stimulus–R–R interval response relations during one held expiration. Pressure changes applied non-invasively (and therefore, safely) to the neck provoke parallel linear changes of baroreceptive carotid artery diameter (Kober & Arndt, 1970), which alter vagal and sympathetic neural outflows and trigger baroreflexes responses. Figure 1 shows American astronaut, Rhea Seddon performing baroreflex research on herself in space (left), a stylized neck pressure profile (A), an actual cardiac R–R interval response (B), and responses of a different astronaut before and during spaceflight (C).

We reported responses of 13 healthy astronauts studied before, during and after two space shuttle missions, in a recent issue of *The*

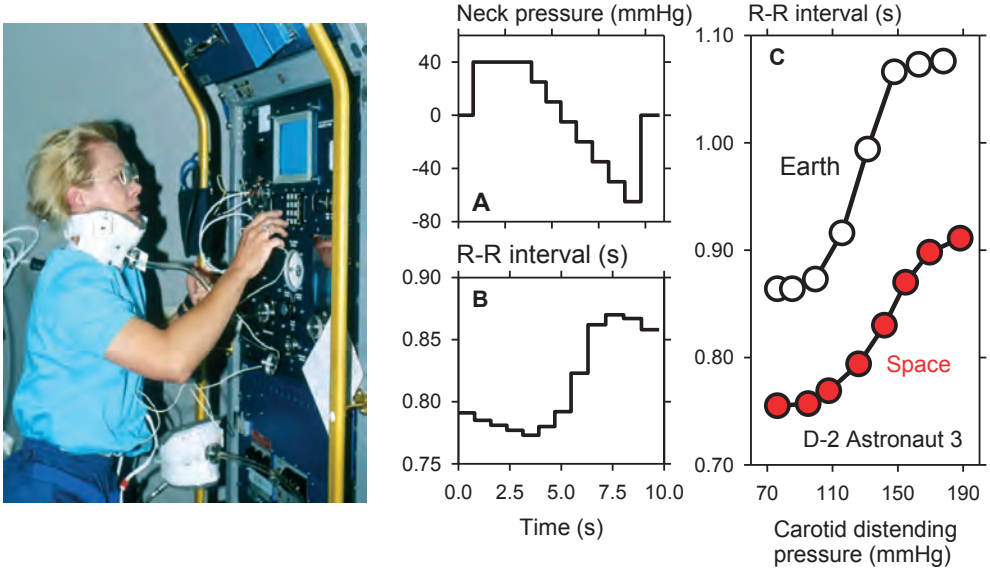

Figure 1. Astronaut Rhea Seddon performing baroreflex research on herself in space, and baroreflex responses of other astronauts on Earth and in space.

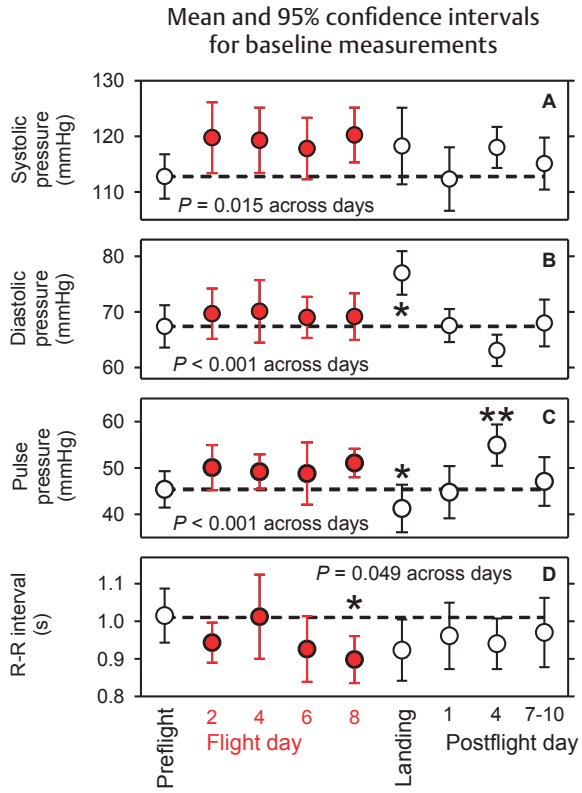

Figure 2. Mean haemodynamic measurements and 95% confidence intervals for all 128 subjects and all sessions.

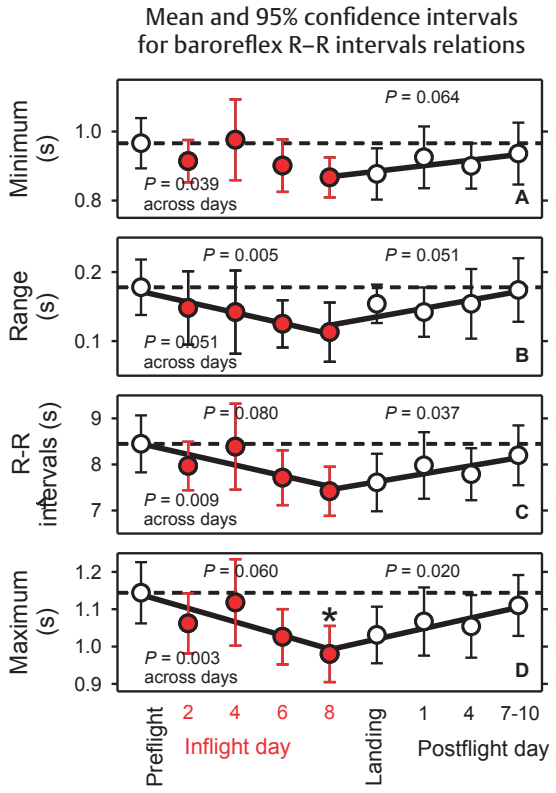

Figure 4. Baroreflex parameters of astronauts before, during and after spaceflight.

Journal of Physiology (Eckberg *et al.* 2010). This research was remarkable in the sense that the number of subjects was larger than nearly all studies conducted on astronauts in space. Figure 2 shows mean (±95% confidence intervals) haemodynamic measurements, with data recorded in space shown in red. Systolic, diastolic and pulse pressures varied significantly across days (repeated measures analysis of variance). Diastolic pressure was significantly higher on landing day than on all other study days (Holm–Sidak test); pulse pressure on landing day was significant lower than on flight day 5, and pulse pressure on postflight day 4 was significantly higher than preflight, landing day and postflight day 1; and mean R–R intervals were significantly lower on flight day 8 than preflight.

Figure 3 shows mean and 95% confidence intervals of baroreflex stimulus–sinus node response relations for all astronauts before and during spaceflight. With the exception of flight day 4, all average relations were lower in space than during preflight measurements. Ninety-five per cent confidence intervals at higher carotid distending pressures did not overlap by flight day 8. Figure 4 shows changes of individual parameters of sigmoidal vagal baroreflex relations for all sessions. In general, all measurements declined steadily as the space mission wore on, and returned towards preflight levels after astronauts returned to Earth.

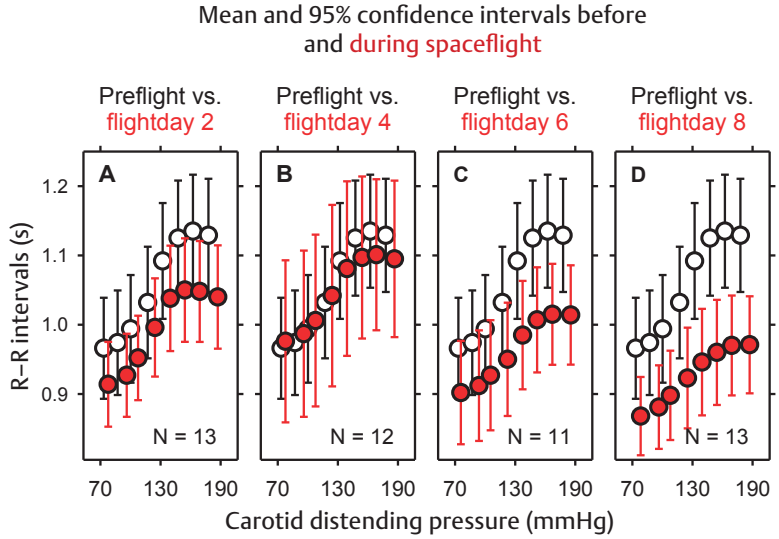

Figure 3. Sigmoidal baroreflex relations before and during spaceflight.

Our study fleshes out changes of baroreflex function in space and extends earlier research (Cox *et al.* 2002), in which sympathetic and vagal baroreflex responses were elicited during spaceflight with Valsalva's manoeuvre. These results, with those of another study of astronauts (Ertl *et al.* 2002), suggest that although humans function very well, exposure to microgravity leads to reduced vagal and augmented sympathetic influences in space. Microgravity exposure reduces

blood volume, atrophies anti-gravity muscles and impairs vestibular function. Progressive impairment of vagal baroreflex function may represent neuroplastic changes occurring in response to major changes of the autonomic milieu in space. As such, these results may provide a unique perspective on short-lived degradation and subsequent restoration of clinically important human baroreflex function.

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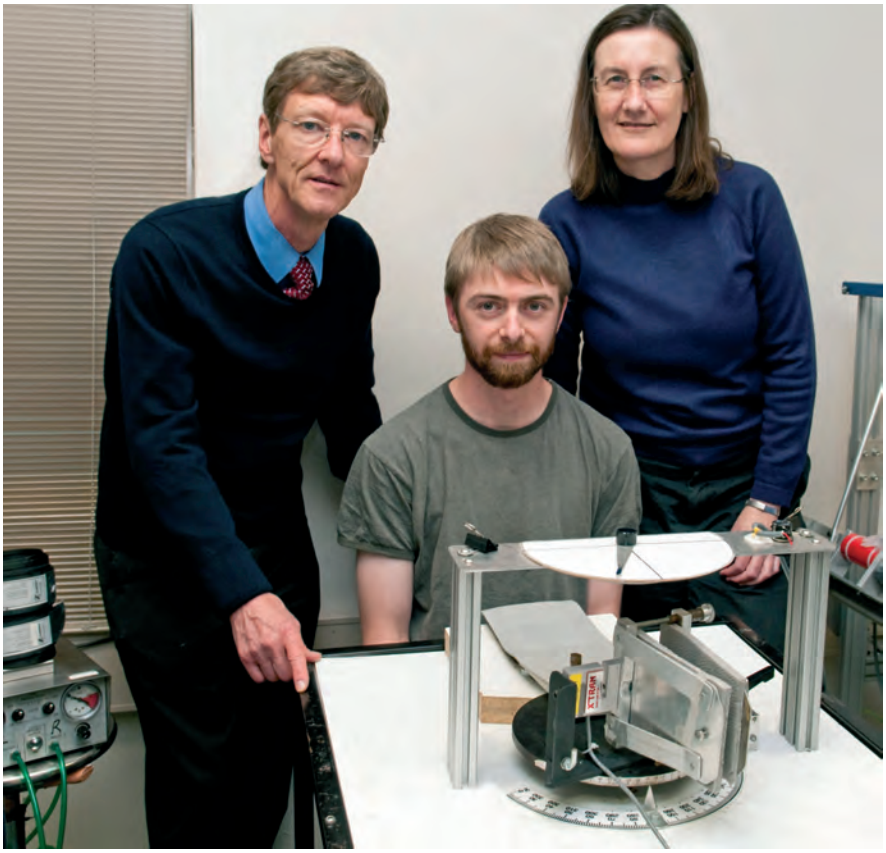
Phantom hands: a window into how we perceive limb position and movement

The senses of limb position and movement are critical to the brain's ability to control movement of the body. These senses are derived from multiple signals and previously it was thought that all these signals came from the muscles, skin and joint. Recent work using 'phantom' limbs in healthy subjects has shown that signals originating in the brain itself also contribute to the senses of limb position and movement.



The authors and experimental equipment. From left to right: Simon Gandevia, Lee Walsh and Janet Taylor.

A healthy person will always know the position and posture of their body in space. Even with our eyes closed we know the position and size of our arms, legs, fingers, head, etc. This is possible because the brain maintains a 'body schema', a representation of our body and its position in space. This body schema cannot simply be a fixed 'map' of our body as our bodies are constantly changing position and size. Some of our body's parameters change slowly. The length of our limbs, the size of our muscles or circumference of our waist changes as we grow, exercise and eat. However, even the increasing length of an adolescent's legs during a growth spurt is very slow compared to the changes that our body schema has to follow when we move our limbs because limb movements cover large distances in fractions of a second. The relatively slow changes to limb length and size could easily be updated in the body schema over time by vision and other senses and, because such changes are small over long periods of time, it is not so critical for the body schema to track these precisely. However, the large and fast changes in joint angle that are associated with every voluntary

movement must be tracked continuously and accurately so that we know at all times where our body and limbs are in space. This ability is critical to the control of body movements. To perform the simple task of picking up a glass of water we must know the position of our fingers, hand and arm, in addition to the location of the glass. It can be said that we know all these things because we can see our fingers, hand and arm as it picks up the glass. That is true, but if you know where the stationary glass is, you can pick it up with your eyes closed. Furthermore, you can still do this if there are unknown obstacles and perturbations between your hand and the glass. This means that your brain can track the position and movements of your arm, hand and fingers without the aid of vision. How is this done?

One way the brain can rapidly update the body schema regarding movements is with information coming from the periphery. Classically the peripheral receptors in the skin form the basis of our sense of touch. In addition to this role, some skin receptors also signal how much the skin stretches around a joint as it moves and thus provide useable information about joint movement and position (e.g. Collins *et al*. 2005). Muscle spindle receptors can signal the length of muscles as well as their rate of change of length. Muscle spindles are sensitive to muscle vibration and classic experiments by Goodwin *et al*. (1972) showed that vibration of limb muscles induces illusory movements of the limbs. From the length of its surrounding muscles, the angle of the joint can be determined and from the rate of change of length of the muscles the velocity of joint movements can be determined. Interpretation of any muscle spindle signal from a contracting muscle is not simple because the size of the signal is modified in complex ways by the fusimotor system. The signal also diminishes if the muscle shortens too rapidly. Receptors located in the joint capsule can also contribute information about joint movement. All these signals travel through large-diameter nerves to the brain, which means that the information gets there very fast, as is required to keep the brain's body schema updated with ongoing movements. These signals from the muscles, skin and joints provide critical information about joint movement, and losing this information results in serious disability (Cole, 1991). However, input from the peripheral receptors is not the only way the body schema is updated during movement.

Figure 1. A photograph of the experimental set-up used in Walsh *et al*. (2010). The subject's right arm rested on a table with the hand fixed into a manipulandum. In the experiment a towel (not present in photograph) covered the subject's right arm so they could not see their forearm, hand and wrist. The manipulandum could be locked into position and a load cell was used to train the subject to perform the efforts before the cuff was inflated. The cuff was inflated to 250 mmHg around the upper right arm. The subject remained relaxed for 30–35 min, during which the ischaemic block developed. After the block was complete the subject performed voluntary efforts with their right arm and controlled the pointer with the left hand to indicate any perceived phantom movements.

Amputees often continue to perceive a limb or body part that has been removed. These sensations are referred to as 'phantoms' and can be explained by the body schema persisting in the brain, despite the limb having been amputated and no longer providing meaningful sensory information about itself. Another interesting thing about phantom limbs is that they can be 'moved'. Often this is described as a phantom which itself is static but which moves along with the remaining part of the limb or a phantom that moves when partially amputated muscles, that were once involved in moving the missing limb, are activated (e.g. Reilly *et al*. 2006). However, some amputees are able to make movements of joints within a phantom that has none of its relevant musculature remaining. For example, an amputee whose arm is amputated at the shoulder may make phantom finger movements.

It is possible to induce temporary experimental phantoms in human subjects. A simple way of doing this for the wrist and hand is to inflate a blood pressure cuff around the upper arm (Fig. 1). This cuts off the blood

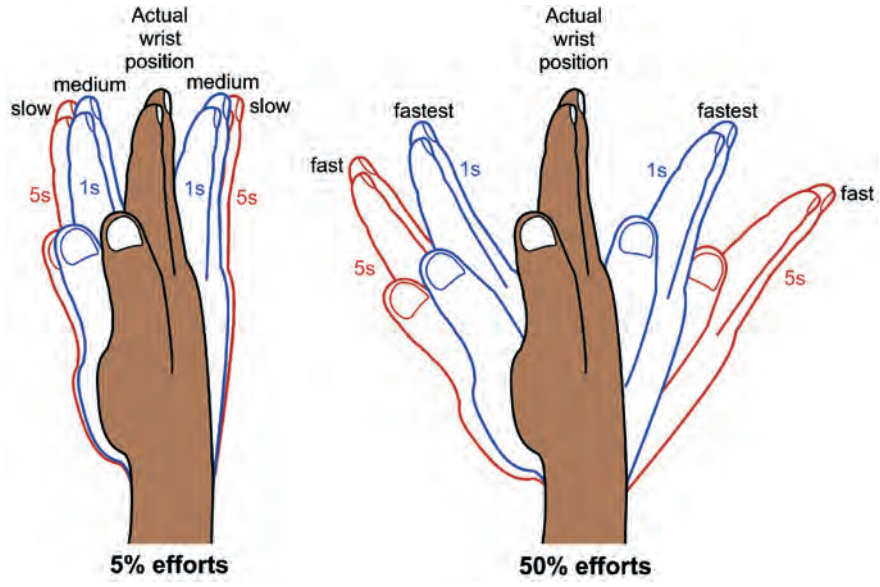


Figure 2. Movements of a phantom hand during voluntary efforts. In our recent study (Walsh *et al.* 2010) subjects had their forearm, wrist and hand anaesthetised and paralysed by a cuff around the upper arm. When the block was complete subjects were asked to make voluntary efforts with their paralysed and anaesthetised wrist and indicate with a pointer any movements that they perceived. The filled hands (index and middle finger are shown) represent the actual position of the subjects' hand. The blue-outlined hands show the mean size of the phantom movements indicated by subjects during a voluntary effort that was 1 s long. The red-outlined hand shows the mean size of the phantom movements reported by subjects during a 5 s voluntary effort. The speeds of the movements produced by the four voluntary efforts shown are ranked by the terms slow, medium, fast and fastest. Subjects indicated that they perceived movements of their phantom which were bigger when they made stronger efforts or longer efforts and faster if they made stronger efforts.

supply to the arm below the cuff. After 30-40 min the arm will become anaesthetised and paralysed. Motor nerves cannot conduct commands to move the arm below the cuff and no sensory information is generated. Despite the lack of sensory information, subjects continue to experience the presence of their anaesthetised and paralysed forearm, wrist and hand. That is, they experience a phantom. We used this method in a recent study (Walsh *et al.* 2010) and once subjects were paralysed and anaesthetised we asked them to make efforts to flex or extend their wrist and to indicate what happened with a pointer. The subjects indicated that when they made voluntary efforts their phantom wrists moved in the same direction as their effort. If they made an effort into flexion with their wrist they perceived their wrist to move into flexion, despite the muscles being paralysed. This sensation was one of continuous movement rather than of the phantom simply adopting a new position. If subjects made longer-duration efforts their phantom wrist moved further and if they made stronger efforts it moved further and faster (Fig. 2).

When we make movements the brain generates central signals that ultimately result in motoneurone output to the appropriate muscles, causing them to contract and move the limb. These signals are commonly referred to as 'motor commands' and our results suggest that information about these commands is used to update the body schema regarding limb movements. There is no sensory information coming back to the brain from the anaesthetised wrist, but while the motor commands cannot get to the paralysed wrist muscles to activate them, they are still generated by the brain and presumably still undergo their normal processing. The idea is that when the brain generates a motor command, information about which muscles are activated, how strongly they are activated, and for how long, is used to update the body schema. This information can give an accurate indication of the movement if there are no unexpected events. This mechanism is likely to be the one that allows amputees to move their phantom limbs.

It is not a new idea that information about motor commands could be used to tell us about the position and movements of our limbs. However, the idea was unpopular for most of the last century, despite the dominance of these signals in oculomotor theory (e.g. Donaldson, 2000). Over the last few years, however, there has been increasing evidence that these signals which originate in the brain combine with those sensory signals from the limbs to give us our complete senses of limb position and movement. The big question now is how do these two classes of signals interact with each other to produce these critical senses that we rely on every time we make a movement.

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Cystic fibrosis: a lesson in chemistry

Paul Quinton and Ruth Muchekehu examine a (micromolecular) sticky problem

Paul Quinton (left) and Ruth Muchekehu

Physiology and medicine usually look to the hard sciences for instruction. However, the pathogenic mucus in the disease cystic fibrosis (CF) may be instructive for physics and chemistry in the forming of mucus gels. The expansion of mucins into mucus gels is largely understood in terms of the exchange of monovalent for divalent cations in anionic mucin networks (Verdugo, 1991). Something may be missing though, since the cause of thick, sticky mucus in CF patients still perplexes physiologists and biochemists more than 60 years after the first descriptions of the disease. Some clues may come from the abnormally thick mucus and defects in bicarbonate secretion (HCO_3^-) found in CF.

Mucin molecules, the main component of gel-forming mucus, are extremely long highly charged anionic polymers that are stored in mucus cell granules at 1/1000 of their final volume after secretion. To effect this tight, pre-secretory packing, the strong electrostatic repulsion of mucin negative charges is neutralized by protons and high concentrations of divalent Ca^{2+}. Until now, the physical chemistry of mucin polymer expansion during secretion relied principally upon a Donnan effect thought to be due to simply exchanging these bound cations for mobile monovalent K^+ and/or Na^+ that almost instantly 'hydrates' the mucin molecules by about 1000-fold (Verdugo, 1991). However, the fluids that accompany mucus secretion in CF are replete with Na^+ and K^+, and yet the mucus afflicting the many glands in CF remains thick and adhesive.

Currently, the thick mucus in CF is generally assumed to be due to an abnormal hyperabsorption of fluid from secreted mucins. For example, it is thought that water is excessively absorbed from mucus secreted onto the airway surface in CF lungs making it difficult to remove. However, many of the organs afflicted by thick mucus in CF do not have this capacity to reabsorb fluids. The facts thus dictate that something is still missing in our understanding of the physics and chemistry of mucus gel expansion. The disease pathophysiology implicates HCO_3^-.

Both mucus and bicarbonate equip the body with a protective gel that coats the surfaces of hollow organs, providing a physical barrier and chemical buffer that guard the epithelial surface. Mucus production must be delicately balanced; too little mucus leaves cells vulnerable to solid and chemical irritants as well as bacterial and viral pathogens, and too much mucus leads to stagnation, inflammation and infections. As the predominant extracellular buffer, bicarbonate (HCO_3^-) must support gastroduodenal defence, suspend bile, stabilize digestive pro-enzymes, impede bacterial binding and serve as a critical adjuvant to antibacterial defensins. It is perhaps no marvel that mucus and HCO_3^- are allies, but are they more intimately involved?

CF provides clues that intrinsically link mucus and HCO_3^-. CF is a hereditary disease caused by mutations in the gene that encodes the cystic fibrosis transmembrane conductance regulator (CFTR) Cl^- channel protein, whose loss of function inhibits both Cl^- and HCO_3^- transport. Concurrent losses of HCO_3^- secretion occur in tissues affected by abnormal mucus in CF, and the loss of HCO_3^- transport seems to correlate with severity of the CF pathology (Choi *et al.* 2001).

In the female reproductive tract, mucus viscosity and bicarbonate change inversely during the menstrual cycle. When HCO_3^- is at its maximum concentration at ovulation, mucus viscosity is minimal, and when HCO_3^- is lowest at the follicular phase, mucus viscosity is at its peak. HCO_3^- douching improves sperm penetration of cervical mucus by reducing the viscosity of cervical mucus. This suggests the coordinated changes in mucus and HCO_3^- are not coincidental, especially given that mucus thinning is absent in women with CF. All these observations imply that HCO_3^- attends mucus viscosity.

How, then, can HCO_3^- affect the physical properties of mucus? We surmise that, normally, secreted HCO_3^- enables mucin expansion by sequestering the bound Ca^{2+} and

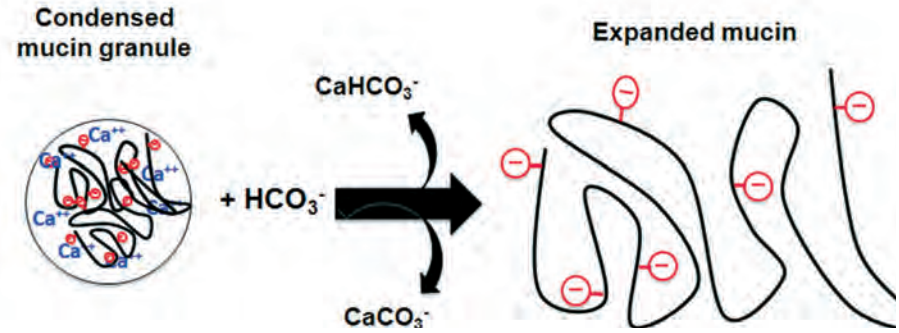

Figure 1. The role of bicarbonate in mucus release. Highly condensed polyanionic mucins are packaged within granules by virtue of high intragranular concentrations of Ca^{2+} (shown) and H^+ that shield negatively charged sites on mucins from electrostatic repulsion. Sequestering Ca^{2+} or buffering H^+ from mucins immediately upon release from the cell allows the electrostatic repulsion of the fixed negative charges to rapidly expand condensed mucins (right side). The presence of extracellular HCO_3^- ensures unsheilding by sequestering the Ca^{2+} and H^+ of mucins. In the absence of HCO_3^-, excessive shielding remains, resulting in less expanded, more viscous mucus.

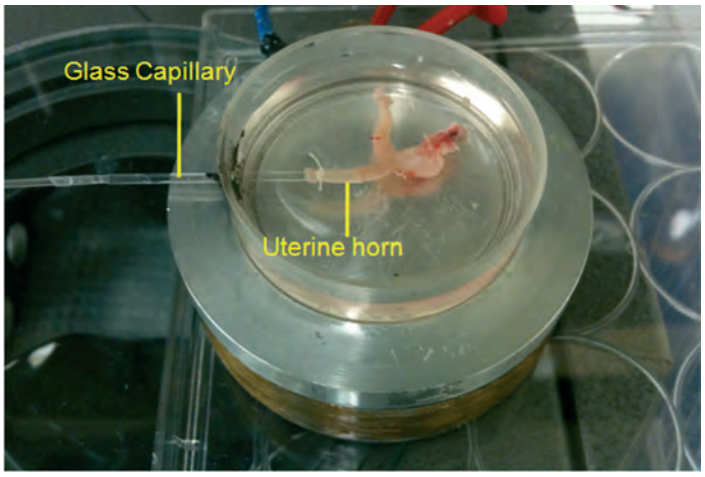

Figure 2. Measurements of fluid secretion. One uterine horn is attached to a glass capillary. The other uterine horn and the vaginal end are ligated to form a closed sac. Agonist-induced fluid secretion forces fluid into the capillary hydrostatically, and the rate of secretion is measured by following the fluid meniscus in the capillary with a microscope micrometer.

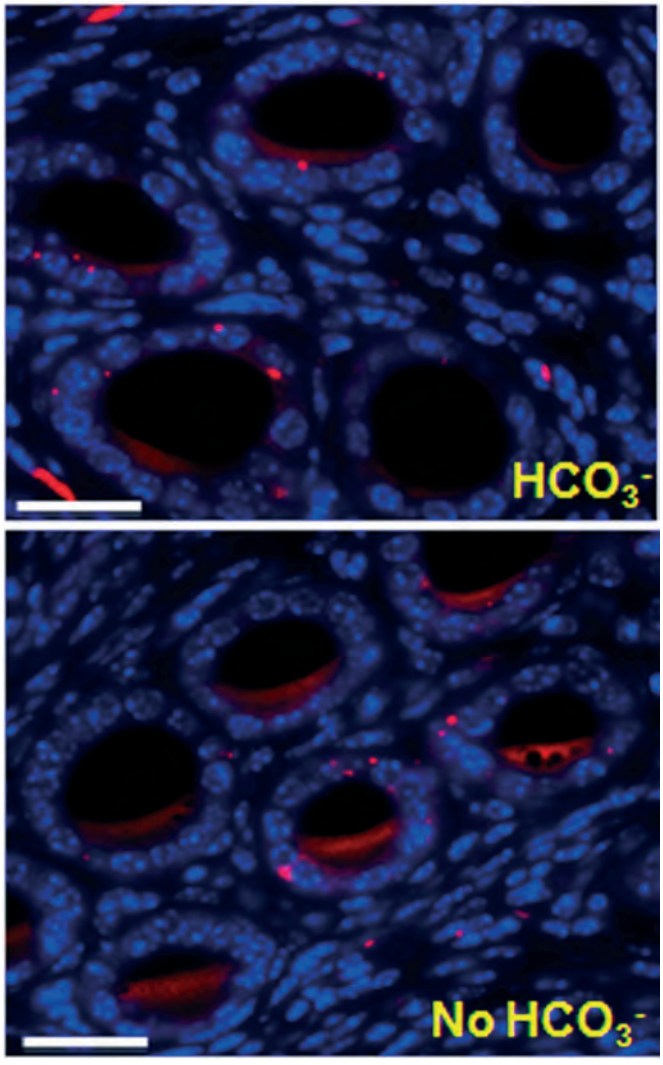

Figure 3. Mucus is retained in the uterine glands in the absence of HCO_3^-. Uterine tissue was stimulated with PGE_2 + carbachol for 20 min before fixing. In the presence of serosal HCO_3^- minimal amounts of mucus remain in the glands. In the absence of serosal HCO_3^-, MUC5B labelling demonstrates significant mucus retained in the lumen of the glands. MUC5B mucin staining (red) counterstained with DAPI (blue) to visualize the nuclei. Scale bar, 25 μm.

H^+ from secreted mucins. This will expose negative charges, enabling electrostatic forces to vigorously and rapidly open the mucin molecule (Fig. 1). That is, HCO_3^- changes the dynamics of mucin expansion by competing with the fixed anions of the mucin molecules for Ca^{2+} and H^+ rather than Na^+ and K^+ competing with Ca^{2+} for the fixed anionic sites on mucins.

To test this notion, we used the female reproductive tract of wild type (WT) and CF ΔF508 mice mounted in a custom-fabricated perfusion chamber. The lumens were perfused and bathed basolaterally with either HCO_3^--replete or HCO_3^--depleted Ringer solution and stimulated to acutely release mucus into the luminal perfusate. In wild type mice, mucus release was severely impaired in the absence of extracellular HCO_3^-. In the CF ΔF508 homozygous reproductive tract, or when CFTR was inhibited pharmacologically in wild type tissues, mucus release was also significantly depressed (Muchekehu & Quinton, 2010).

Cyclic adenosine monophosphate (cAMP)-mediated fluid secretion is depressed in CF and may be important for mucus discharge. We tested the importance of fluid secreted from the reproductive tract by canulating one horn of the closed uterine sac with a glass capillary (Fig. 2). Fluid secretion was monitored by the displacement of the air–liquid meniscus in the capillary. In contrast to mucus release, stimulated fluid secretion was not dependent on HCO_3^- or on CFTR function under these conditions. Moreover, without HCO_3^-, mucus remained 'trapped' in the lumens of the uterine glands (Fig. 3) (Muchekehu & Quinton, 2010).

These findings present a new role for HCO_3^- as a critical element in mucus release and in the regulation of mucus viscosity generally. Mucus thinning at the ovulatory stage of the menstrual cycle allows the passage of sperm through the reproductive tract, but this role is not limited to the reproductive tract as mucus

release in the small intestine is also HCO_3^- dependent (Garcia *et al.* 2009). Moreover, the principal gel-forming mucin of the gut (MUC 2) is not the same as in the uterus (MUC 5B); and the viscosity of the third major gel-forming mucin (MUC 5AC) during stimulated secretion from cultured cells is markedly dependent on extracellular HCO_3^- levels (Chen *et al.* 2010). Adding to this, the common viscid mucus pathology affecting different mucins secreted by disparate organs in CF all strongly imply that HCO_3^- is a common and necessary attendant to normal mucus expansion.

In a certain sense then, the tables of the sciences may be turned as the physiology of the female reproductive tract and the pathophysiology of CF offer new lessons for chemistry and physics on how mucin polymer gels expand.

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Sympathetic nervous system and volume-regulatory hormones: interactions during dehydration

Sympathetic nerve activity and volume-regulating hormones defend blood pressure and blood volume during dehydration. Recent findings showing interactions between these systems give us further insight into the complex adaptations to dehydration.

The ability of the human body to adapt to and protect from dehydration has fascinated physiologists for centuries and yet new insight continues to be gained into the mechanisms involved. Further understanding of these interactions has broad implications in healthy populations, from the athlete to the elderly, as well as patient populations, from the acutely dehydrated surgical patient to the acutely or chronically ill medical patient.

Nisha Charkoudian (left) and Jennifer Rabbitts.

Dehydration, along with the associated changes in blood volume and plasma osmolality, elicits a range of physiological responses which must be integrated in order to protect blood pressure and blood volume, thus maintaining perfusion pressure to vital organs such as the brain. In a dehydrated individual, the sympathetic nervous system is activated: increases in cardiac sympathetic activity cause increases in heart rate and stroke volume, while increases in vascular sympathetic activity cause vasoconstriction and maintenance of arterial pressure via increased peripheral resistance. Simultaneously, the renal volume-regulating system is also activated, leading to release of volume-regulating hormones, including angiotensin, aldosterone and vasopressin, which minimize losses in plasma volume via antidiuretic effects on the kidney.

Recently, evidence has emerged that there is an interaction between volume-regulating hormones and the sympathetic nervous system which is not yet fully understood. Many of the volume-regulating hormones have been shown to alter sympathetic neural control mechanisms in several animal models (Fink, 1997; Hasser *et al.* 2000). For example, Cox and Bishop found that angiotensin administered exogenously to rabbits affects sympathetic nerve activity (Cox & Bishop, 1991). Furthermore, Matsukawa *et al.* (1991) showed that exogenously administered angiotensin II has sympathetic neural effects in humans.

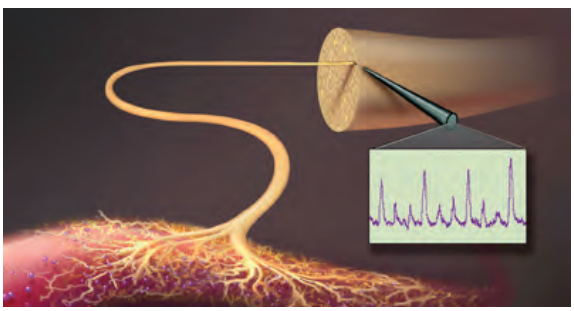

Figure 1. Dagrammatic representation of the placement of the microelectrode in the muscle sympathetic nerve fibres and the recording of sympathetic nerve activity.

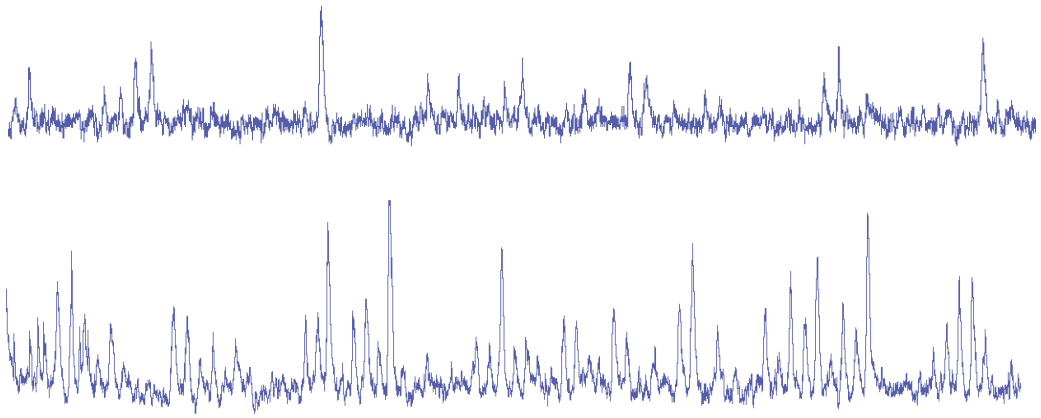

Figure 2. Muscle sympathetic nerve activity recordings from a single representative subject on two separate days, during euhydration (top recording) and dehydration (bottom recording).

We were interested in evaluating the influences of endogenous angiotensin in the context of human dehydration. In our first study to address this goal we wanted to know whether the elevation in angiotensin during dehydration is causing neural changes during dehydration in humans. Our hypothesis was that endogenous angiotensin II has a mechanistic role in some of the sympathetic neural changes that are observed in dehydration in normal humans.

In the lab we are able to measure the electrical activity in sympathetic nerve fibres in humans, specifically postganglionic sympathetic fibres innervating the blood vessels in skeletal muscles (known as muscle sympathetic nerve activity (MSNA)). Although this technique is technically challenging, the data obtained can give unique insight into the beat-to-beat function of the sympathetic nervous system. Figure 1 is a diagrammatic representation of the placement of the microelectrode in the sympathetic nerve fibres and the recording of sympathetic nerve activity. We commonly use the peroneal nerve which is next to the knee and innervates blood vessels of skeletal muscle of the lower leg and foot. Each one of the upward peaks in the MSNA recording is called a burst of sympathetic nerve activity and represents a collection of action potentials in vasoconstrictor nerve fibres. Figure 2 shows actual MSNA recordings in a subject. MSNA is quantified as burst frequency, burst incidence (which controls for difference in heart rates) or total activity (taking into account both burst number and size).

In order to test our hypothesis regarding the role of angiotensin in mediating changes in the sympathetic nervous system during dehydration, we measured MSNA, heart rate and continuous blood pressure in 18 healthy young male and female subjects during euhydration and during dehydration induced by 24 hour fluid restriction (Rabbitts *et al*. 2009). Figure 2 shows two tracings in the same individual on two different study days, one during euhydration and one during dehydration, illustrating that MSNA is increased during dehydration. With blockade of angiotensin II receptors, this effect was reversed, confirming that in addition to its known volume-regulating effects, angiotensin does mediate some of the sympathetic effects of dehydration. Thus, for the first time in humans we have shown that endogenous angiotensin has sympathetic neural effects which further protect blood pressure during dehydration.

This interaction between the volume-regulating hormones and the sympathetic nervous system to protect blood pressure could have implications in a spectrum of conditions associated with volume depletion and is not yet fully understood. In terms of sympathetic neural effects, the roles of other endogenous hormones released during dehydration in humans, such as aldosterone and vasopressin, await future study.

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Heart rate regulation during exercise

Exercise-mediated increases in heart rate are elicited by a complex interaction of multiple neural control mechanisms. We have demonstrated that the activation of metabolically sensitive receptors in skeletal muscles (muscle metaboreflex) increases cardiac sympathetic nerve activity in humans, an effect that can be masked by elevations in parasympathetic tone. Thus, the muscle metaboreflex contributes importantly to the regulation of the heart during exercise. These findings have implications for disease conditions associated with low cardiac parasympathetic tone and exaggerated feedback from the exercising muscles, such as chronic heart failure.

Profound alterations in cardiovascular regulation must occur in order to sustain exercise for more than a few moments. To meet the increased metabolic demand of the active muscles, local blood flow must increase. Consequently, cardiac output increases and blood flow is redirected to the contracting muscles by vasoconstriction in regions such as renal and splanchnic vascular beds. Both the sympathetic and parasympathetic branches of the autonomic nervous system are important in mediating this co-ordinated response and the elucidation of the underlying regulatory mechanisms has engaged researchers for a century. It is now established that the cardiovascular responses to exercise result from the activation and interaction of both central and peripheral neural mechanisms. Feed-forward signals from the brain (e.g. insular cortex), known as central command, arise in parallel with descending motor drive to the exercising muscles and converge on the cardiovascular areas of the brain (e.g. nucleus tractus soltarii). Concomitant feedback from the active muscles via small group III and IV afferent nerves provides feedback to these cardiovascular areas in response to both mechanical and metabolic stimulation. As a consequence, the arterial baroreflex is reset to the prevailing heart rate and blood pressure established during exercise and this plays an important role in the neural regulation of the cardiovascular system during physical activity.

The dissection of the discrete contribution made by each of the neural control mechanisms implicated in the cardiovascular response to exercise is challenging,

From upper left and clockwise: James Fisher, Paul Fadel and Niels Secher.

particularly in human studies where invasive methods are limited. However, an array of ingenious experimental approaches (e.g. neuromuscular blockade, deep brain stimulation, tendon vibration and inflatable trousers) along with deductive reasoning has brought insight to this research area. One approach that is commonly used in humans to investigate the cardiovascular effects of activating metabolically sensitive skeletal muscle afferents (muscle metaboreflex) involves the occlusion of the circulation to the exercising muscles just prior to the end of exercise and keeping it in place for a period of exercise recovery. This 'post-exercise ischaemia' traps the metabolites produced during exercise within the muscles after the contraction and effectively isolates the muscle metaboreflex from the exercise-induced activation of central command and mechanically sensitive muscle afferents. The circulatory occlusion can be performed simply by inflation of a cuff around the limb, proximal to the exercising muscles, as first described by Alam & Smirk (1937). Alarmingly these pioneering investigators also noted that *'a forearm may be devascularied and the circulation arrested by plunging it into a bath of mercury depth of about 12 cm. above the elbow'*, but thankfully this approach has not been adopted!

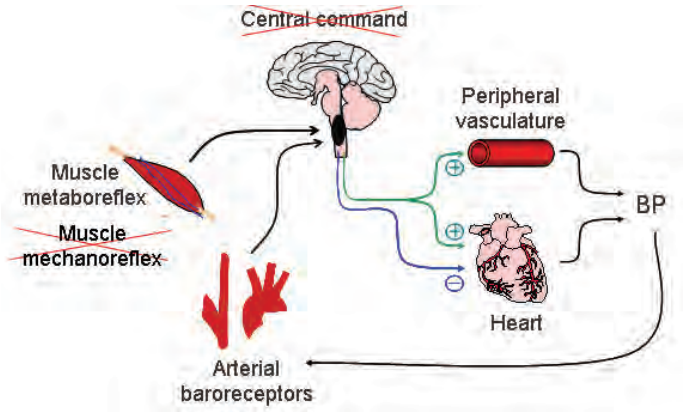

Figure 1. Schematic showing hypothetical integration of muscle metaboreflex and arterial baroreceptor feedback to the central nervous system during post-exercise muscle ischaemia. Previous studies have clearly demonstrated that activation of the muscle metaboreflex during post-exercise ischaemia causes an increase in sympathetic vasoconstrictor outflow to the peripheral vasculature (green arrow). Our findings demonstrate for the first time in humans, that concomitant increases in sympathetic outflow to the heart are dampened by cardiac parasympathetic reactivation, probably due to arterial baroreceptor activation and/or the loss of central command and muscle mechanoreceptor input.

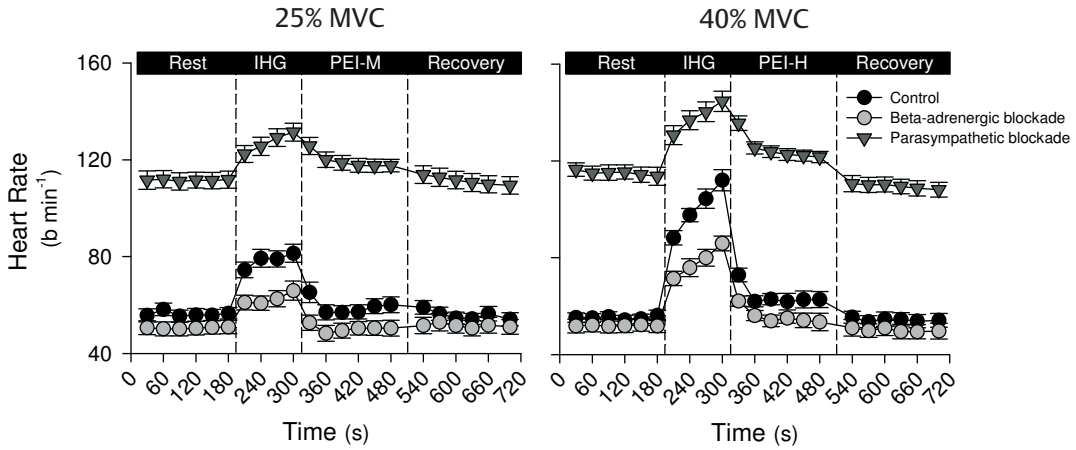

Figure 2. Heart rate during isometric handgrip (IHG) and post-exercise ischaemia (PEI) under control, β-adrenergic blockade and parasympathetic blockade conditions. PEI-M, PEI following 25% IHG; PEI-H, PEI following 40% IHG; MVC, maximal voluntary contraction. Adapted with permission from Fisher *et al*. (2010).

Intriguingly, heart rate consistently falls to baseline values during post-exercise ischaemia while exercise-induced increases in blood pressure and vasoconstrictor sympathetic nerve activity remain elevated. This has led to the notion that the muscle metaboreflex does not influence heart rate, but raises blood pressure via sympathetically mediated peripheral vasoconstriction (Rowell & O'Leary, 1990). An alternative explanation is that an overwhelming effect of parasympathetic reactivation slows the heart during post-exercise ischaemia, and masks the influence of sympathetic nerve activity on the heart (Fig. 1). This may occur for two reasons. First, the inhibitory effects of central command and mechanically sensitive skeletal muscle afferents on parasympathetic activity are lost in the transition from exercise to post-exercise ischaemia. Second, the elevation in blood pressure during post-exercise ischaemia could stimulate the arterial baroreceptors and reflexively increase parasympathetic tone. As such, this parasympathetic reactivation could obscure any metaboreflex-mediated increase in cardiac sympathetic nerve activity which would otherwise accelerate heart rate (O'Leary, 1993). If this were the case, then the elimination of cardiac parasympathetic tone during post-exercise ischaemia should reveal an increase in heart rate, as a muscle metaboreflex-mediated increase in cardiac sympathetic nerve activity would be unmasked.

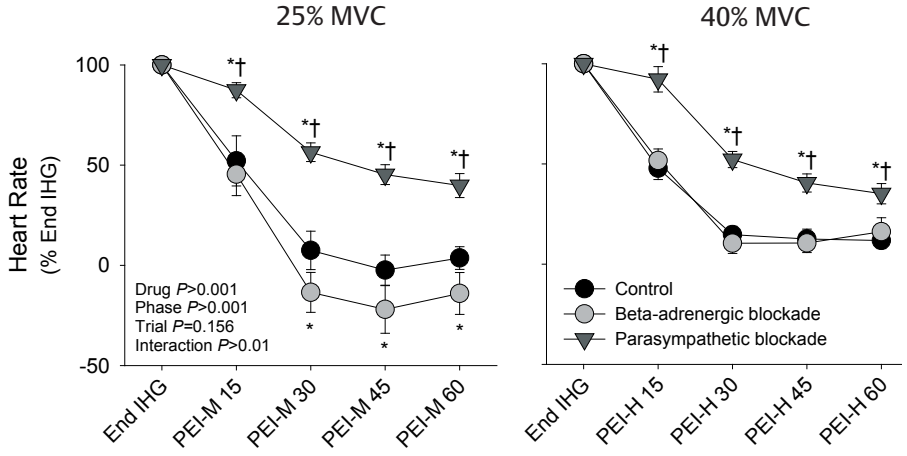

Figure 3. Heart rate during the first minute of post-exercise ischaemia expressed as a percentage of end isometric handgrip values (End IHG), under control, β-adrenergic blockade and parasympathetic blockade conditions. PEI-M, PEI following 25% IHG; PEI-H, PEI following 40% IHG. Time points represent 15 s averages. $^{*}P < 0.05$ *vs*. control, †$P < 0.05$ *vs*. β-adrenergic blockade. Adapted with permission from Fisher *et al*. (2010).

To investigate the potential influence of sympathetic nerve activity on heart rate during post-exercise ischaemia we used a pharmacological approach previously performed in exercising dogs (O'Leary, 1993). The cardiovascular responses to two intensities of muscle metaboreflex activation were compared during post-exercise ischaemia under control conditions, and after parasympathetic and β-adrenergic blockade (Fisher *et al.* 2010). As expected, blood pressure was increased from rest during moderate metaboreflex activation and further elevated during high-intensity metaboreflex activation in all conditions. We observed that during moderate-intensity metaboreflex activation under control (no drug) conditions, heart rate was negligibly elevated from rest (+3±2 beats min^{-1}); however, when this was repeated following parasympathetic blockade (using the muscarinic blocker glycopyrrolate) an increase in heart rate was observed (+8±2 beats min^{-1}; Fig. 2). Interestingly, when high-intensity metaboreflex activation was performed an elevation in heart rate was noted, which was attenuated with β-adrenergic blockade but was unchanged with parasympathetic blockade. Collectively, these findings suggest that the muscle metaboreflex increases cardiac

sympathetic nerve activity during post-exercise ischaemia in humans; however, it requires a robust muscle metaboreflex activation to offset the influence of cardiac parasympathetic reactivation on heart rate.

We also observed that the rate at which heart rate recovered from the end of exercise during post-exercise ischaemia was slower with parasympathetic blockade, compared with the control or β-adrenergic blockade conditions (Fig. 3). We presume that this sluggish heart rate recovery is due to gradual withdrawal of cardiac sympathetic nerve activity following the rapid loss of inputs from central command and muscle mechanoreceptors during sustained muscle metaboreflex activation. These data are important because a delayed recovery in heart rate following exercise is a powerful independent predictor of mortality even in low risk patient populations (Cole *et al.* 1999), an effect that is linked to the reactivation of parasympathetic activity (Imai *et al.* 1994). Our findings broadly support this concept, and further suggest that in the absence of parasympathetic reactivation, increased cardiac sympathetic nerve activity may also contribute to a delayed post-exercise recovery of heart rate. These data may be clinically relevant for disease conditions associated with altered skeletal muscle afferent sensitivity and low cardiac parasympathetic tone, such as chronic heart failure.

In summary, these findings suggest that isolated muscle metaboreflex activation increases cardiac sympathetic nerve activity during post-exercise ischaemia in humans, but to have an effect on heart rate, robust muscle metaboreflex activation is needed to offset cardiac parasympathetic reactivation.

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Bebowlered Barcroft

In the Oxford Dictionary of National Biography (2004), John West's article on the Cambridge physiologist Joseph Barcroft (1872–1947), includes an anecdote recounted by CG Douglas, another respiratory physiologist. In the First World War Barcroft, being a Quaker, was a non-combatant but he went to the French front in connection with his work on the effects of gas poisoning. Although he insisted on standing in a prominent position at a crossroads, no one fired at him. It was suggested that his bowler hat may have unsettled the gunners.

Ann Silver

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University of Oxford, UK, 11–14 July
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Scientific Meetings – 2012

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Physiology 2012
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The Journal of Physiology Symposia 2011

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Satellite Symposium at the 31st International Symposium on Intensive Care and Emergency Medicine
Brussels, Belgium, Tuesday 22 March

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Experimental Biology 2011,
Washington, DC, USA, Sunday 10 April

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Physiology 2011 Wednesday 13 July

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The K_{ATP} channel is a molecular sensor of atrophy in skeletal muscle

In a recent study in *The Journal of Physiology* we demonstrated for the first time that the metabolically regulated ATP-sensitive K^+ channel (K_{ATP}) can regulate the atrophic process in fast- and slow-twitch rat skeletal muscle. The K_{ATP} channels are normally expressed in the sarcolemma and in mitochondrial membrane, sensing and coupling intracellular nucleotide composition with K^+ efflux and membrane potential. Channel opening occurs in response to a reduction in the ATP/ADP ratio during metabolic stress, which is often associated with abnormal Ca^{2+} movements across the cell membrane or inner mitochondrial membrane.

The K_{ATP} macromolecule was first discovered in 1983 in cardiomyocytes and later found in pancreatic beta cells, vascular myocytes and more recently in neurons (Flagg *et al.* 2010). The channel belongs to the ABC transporter superfamily: it is an octameric complex formed by the inwardly rectifying K^+ channel subunits (Kir6.1 and Kir6.2) and the regulatory sulfonylurea receptor subunits (SUR1, SUR2A and SUR2B). The SUR subunits carry the binding site for drugs and nucleotides as well as phosphorylation sites. Our previous reports showed an intense K_{ATP} channel activity also in mouse, rat and human fast-twitch skeletal muscles in isolated membrane patches in the absence of intracellular ATP (Tricarico *et al*. 1999; Flagg *et al.* 2010). In resting un-stimulated fibres, K_{ATP} channel activity contributes a few millivolts (3–4 mV) to the resting potential; however, large repolarizing K_{ATP} channel currents are observed following insulin stimulation or high-frequency action potential firing, thereby reducing fibre excitability during muscle fatigue. K_{ATP} channels therefore save the energy pool during metabolic stress and regulate glucose uptake into the fibres. Secondary defects in channel subunits are responsible for insulin

Domenico Tricarico

resistance and for a neuromuscular disorder known as hypokalaemic periodic paralysis.

We now provide evidence that the K_{ATP} channels play a role in skeletal muscle plasticity, which is the ability of the tissue to adapt to new conditions such as disuse through changes in muscle fibre phenotype composition, fibre diameter and cellular metabolism. We made several observations: first, the molecular composition and properties of the K_{ATP} channels are muscle phenotype dependent and muscle specific. This means that the channel properties are related to the speed of contraction and strength, which are muscle phenotype-dependent properties, but are also related to morphological characteristics of the muscles such as length and mass, and with their anatomical location. In this respect, we found higher expression/activity of the Kir6.2/SUR2A or Kir6.2/SUR1 subunits in fast-twitch muscle as compared with slow-twitch muscle phenotypes and differences in the expression/activity of the K_{ATP} channel subunits have also been observed within fast-twitch muscle types (Tricarico *et al*. 2006). High expression of the SUR1 subunit has been observed in the flexor digitorum brevis muscle of the rat, which is a fast-twitch muscle with elevated oxidative metabolism devoted to the rapid movements of the extremities, but also in a slow-twitch soleus muscle, which has postural function. Second, in an accepted animal model of muscle disuse, we demonstrated that the characteristic slow-to-fast fibre transition occurring in the slow-twitch muscle is associated with an up-regulation of K_{ATP} channel subunits, while down-regulation of the Kir6.2/SUR1 subunits correlate with a reduction of the fibre diameters leading to extensive atrophy. The atrophy of fast- and slow-twitch rat skeletal muscle was also pharmacologically induced *in vitro* by glibenclamide, a widely used anti-diabetic drug that blocks the Kir6.2/SUR1 channel subunits. The effects of this drug were prevented by diazoxide, a well-known Kir6.2/SUR1 channel opener, supporting the involvement of this channel in the observed phenomenon. All these findings corroborate the idea that K_{ATP} channels sense the changes in the muscle phenotype and in the fibre trophism (Tricarico *et al.* 2010). Similar effects of glibenclamide and diazoxide were observed in other cell lines expressing Kir6.2/SUR1 subunits (Maedler *et al*. 2004, 2005).

Atrophy is a condition affecting both fast- and slow-twitch muscles, often showing different degrees of damage depending on muscle type and function. It is normally slowly reversible; for example, several months are needed to recover muscle strength and morphology in healthy individuals following partial arm or leg immobilization. Such immobilization can, in severe cases, lead to an irreversible impairment of muscle function. Atrophy is also observed following exposure to toxins, overdose of certain chemo-therapeutic drugs or corticosteroids abuse. It is a common sympton of the cachexia associated with these and other pathophysiological conditions. This process is generally considered to be caused by an imbalance between protein synthesis and degradation, in favour of the latter. Knowledge of the pathways responsible for atrophy is essential for prevention and appropriate therapy. Several intracellular factors responsible for atrophy have been identified that lead to the activation of proteolytic mechanisms and inhibition of protein synthesis (Sandri, 2008).

Our emerging idea is that K_{ATP} channel activity also has a role in the regulation or induction of the atrophic process in skeletal muscle. Generally, K_{ATP} channel opening, if coupled to the energy demand of the cells, is considered protective for the cells and mitochondria, while irreversible channel closure is cytotoxic. Therefore, SUR1 inhibitors may induce atrophy or contribute to the atrophic process in skeletal muscle fibres expressing this subunit. This is of relevance considering the prescribed combined anti-diabetic and chemo-therapeutic drug therapy for the treatment of diabetic patients affected by cancer or bacterial/virus infections.

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IUPS Congresses

I doubt The Society has any regrets (yet) about the optimism that led to its bid in 2005 for the XXXVII IUPS Congress to be held in Birmingham in 2013, twenty years after the XXXII Congress in Glasgow. None-the-less, a tale or two from some past Congresses may concentrate the collective mind. No matter how exciting the science, recollections can be coloured for good or ill by practical issues. *Perhaps there are other physiologists with useful memories to share*.

Leiden

At the Leiden Congress in 1962 no one was around to prevent early arrivals from bagging other people's Poster Board should they dislike their allocated site. I was displaced to a Board outside the Gents: this ensured a continuous, but not fully representative, audience. We had our lunch in two enormous marquees. One night a tremendous gale damaged one of these so badly that it was considered unsafe. This meant that everyone had to crowd into the other, which had also been slightly torn. Most participants gobbled down their food as fast as possible and made a rapid retreat. Not so the British, who phlegmatically took their time. John Phillis and family were camping their way to Italy where they were to catch a boat home to Australia. He had to miss his session to get his bent tent repaired before nightfall.

Paris

The 1977 Congress in Paris was memorable on several counts. On the first day, the thermoregulators couldn't find the theatre specified for their opening lecture, so appropriated one they happened upon. Responding to the speaker's request for a pointer, the projectionist produced a length of plastic moulding that formed a U shape when raised. Just before the lecture ended a man staggered in with an almost unliftable spar. When we left the theatre the same man was outside on his knees trying to saw a plank into more manageable lengths. Paris was also memorable for the reception in the barely finished Pompidou Centre. The programme note saying it was unsuitable for children under 12 was taken to mean a dearth of child-friendly food, not that they risked being trampled under foot. And not just the children – I was forced forwards towards the buffet by the press of the crowd, my hand ending up in some paté – and that was the sum total of my 'refreshments'.

Glasgow

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

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

Ann Silver

The 'why's' of Western blotting. Part I

Electrophoresis of proteins and Western blot is a well-established biochemical technique that is now widely used in other disciplines, including physiology. Typically a lab will have its own established protcols, handed down from generation to generation. Scores of research students will have learnt the technique, diligently following their local step-by-step protocol. Although the 'how to' of Western blotting is disseminated in this manner, the 'why' is often regretfuly neglected. This short *Techniques* series will focus on the latter, and was commissioned in response to a request from a research student who found her 'why' questions unanswered. In this first article, Patricia Leoni, of Imperial College London, explains the principles of protein electrophoresis.

Separation of proteins by electrophoresis

The electrophoretic properties of proteins have been used in research since the early 1930s (Tiselius, 1937). The most useful developments in the field occurred in the sixties with the description of discontinuous buffer systems, the use of polyacrylamide as support medium and the use of detergents. The separation of proteins by electrophoresis is one of the most useful techniques for biomedical research to separate and identify proteins in complex mixtures.

Five of the twenty amino acids which determine the primary structure of proteins are highly ionized and therefore charged. Lysine, arginine and histidine are positively charged, glutamic acid and aspartic acid are negatively charged (Fig. 1).

The degree of ionization, and hence the charge, depends on the pH. At most pH values proteins carry a positive or negative charge,

Patricia Leoni

depending on the content of these acidic and basic amino acids. The pH at which the positive and negative charges are in balance so that the net charge of the protein is zero, is the isoelectric point.

Positively and negatively charged proteins, as all charged particles, migrate in an electric field (Fig. 2).

The electrical properties of proteins have been successfully used to separate complex mixtures of many proteins. It is possible to separate proteins electrophoretically in free solution; however, this has some disadvantages, in particular convective and diffusion effects which broaden the protein bands.

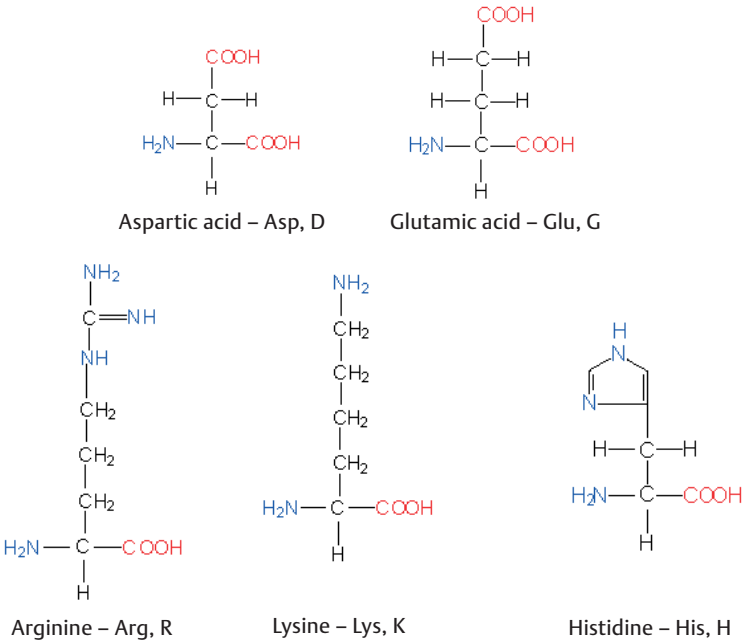

Figure 1. Chemical structure of charged nucleic acids.

The use of porous gel matrices such as starch, agarose and polyacrylamide minimizes these effects and adds the possibility of molecular sieving so that both size and charge are used to optimize separation. Other polymers such as Duracryl have been developed for use as a matrix but are not widely used.

Electrophoresis on acrylamide gels

Polyacryamide gels are non-ionic polymers of acrylamide (CH_2=CH-CO-NH_2) and a cross-linking co-monomer *N*,*N*-methylene bis-acrylamide (CH_2-CH-CO-NH-CH_2-NH-CO-CH=CH_2). Acrylamide is a potent neurotoxin and care must be taken during the handling of the monomer solution. Once polymerized it is no longer toxic.

The gels are transparent, chemically inert and stable over a wide range of pH, temperature and ionic strength. The most important advantage of these gels is that the pore dimensions can be varied simply by increasing the monomer and cross-linking agent concentration in order to optimize it for the separation of proteins of different sizes.

Two parameters are used to describe the gel composition:

%T = acrylamide monomer + cross-linking agent as % weight/volume

%C = percentage of cross-linking agent of the total monomer

The size of the pore can be adjusted by varying the amounts of acrylamide and bis. As %T increases the pore decreases; however, the increase of cross-linking agent over certain values can cause the three-dimensional structure of the gel to be disrupted and the gel can become opaque. Fortunately several commercial companies (e.g. National

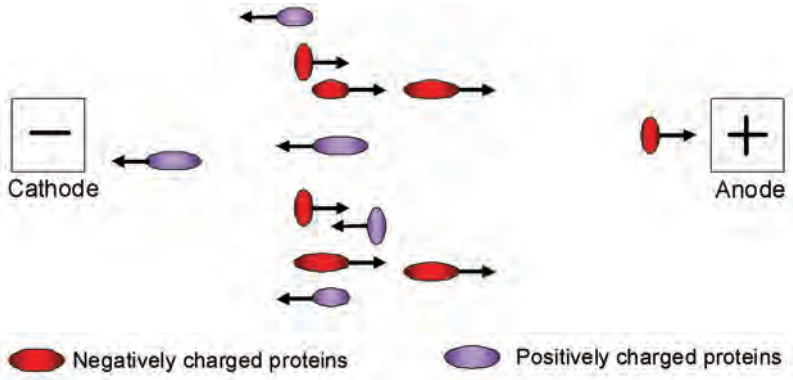

Figure 2. Migration of proteins during electrophoresis.

Diagnostics, Bio-Rad, Sigma, Fisher Bioreagents, GE Healthcare, Roche) provide ready-made, liquid or solid mixtures optimized for protein separation. The most commonly used brands offer acrylamide: bis-acrylamide mixes in three different proportions:

Acrylamide: Bis-acrylamide 37.5:1, with 2,6% of cross-linking agent suitable for the separation of high molecular weight proteins.

Acrylamide: Bis-acrylamide 29:1, with 3.3% of cross-linking agent suitable for the separation of a wide range of molecular weight proteins.

Acrylamide: Bis-acrylamide 19:1, with 5% of cross-linking agent suitable for the separation of low molecular weight proteins.

Gradient gels

The range of molecular weights that can be separated on a gel can be expanded by using gels containing a concentration gradient. These gels have the added advantage of producing sharper protein bands; however, they are cumbersome to prepare in the lab; they require additional equipment and there are difficulties with reproducibility. It might be more practical, if possible, to purchase pre-cast gradient gels. The most usual composition of these gels is 5%–20%T, 2.6%C; the molecular weight range of proteins that can be separated is 10–200x103 kDa. Polymerisation occurs in the presence of free radicals provided by ammonium persulfate in a reaction catalysed by tetramethylethylenediamine (TEMED). The advantage of using ammonium persulfate rather than other catalysts is that it migrates in the same direction but faster than the molecules of interest. The presence of oxygen, which traps free radicals, inhibits polymerization. In some cases it might be useful to remove most of the oxygen by deaeration using a water vacuum pump or by bubbling nitrogen for a couple of minutes.

The amounts of ammonium persulfate and TEMED must be calculated to allow polymerization in approximately 2 hours or longer; although many labs cut corners and use shorter times, these might lead to the formation of short polymer chains and lack of elasticity.

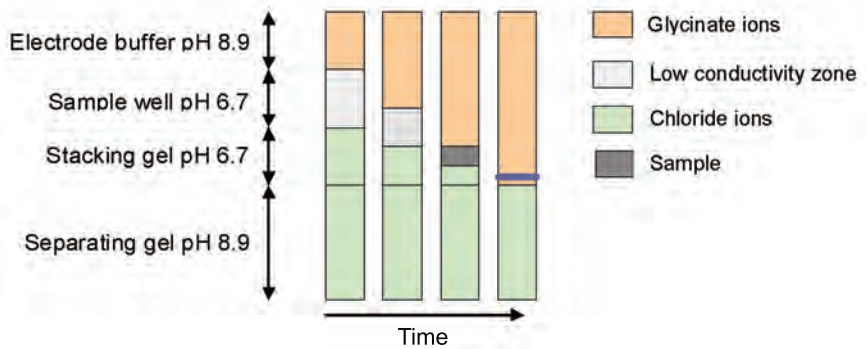

Figure 3. Pattern of protein migration in a discontinuous buffer system.

Electrophoresis of native proteins

In situations where it is desirable to retain the biological activity of proteins, such as enzymatic activity and protein–protein interactions, the separation is carried out using a non-denaturing (native) gel of a suitable concentration and buffer with a pH dependent on the size and charge of the proteins of interest.

The charge of the proteins being separated depends on the pH of the buffer used. At a pH close to their isoelectric point they are prone to precipitate, at pH above 10 and below 3 proteins are unstable due to deamidation and hydrolysis, so these pH ranges should be avoided.

If biological activity needs to be assessed following electrophoresis, the separation should be carried out at a pH at which the protein is active. In selecting the pH of the running buffer it is important to remember that acidic and basic proteins will carry opposite charges and will migrate in opposite directions. Basic proteins need to be separated under acidic conditions and they need to be applied at the anodic end. Most proteins will be negatively charged in alkaline pH and will migrate towards the anode during electrophoresis.

The main disadvantage of using a single buffer in an electrophorectic separation is that it is not suitable for analysis of dilute samples when relatively large volumes are needed. Samples must have a concentration greater that 1µg μl^{-1} in order to allow the use of a very small volume of sample; if samples are more diluted a discontinuous buffer system is required.

Polyacrylamide gel electrophoresis using discontinous buffer systems

This method is the one that is most commonly used. In this technique, discontinuities in the voltage and pH are introduced by using buffers of different composition and pH in different parts of the gel. A major advantage of a biphasic buffer system is its ability to concentrate proteins in dilute samples into a narrow stack. The system developed by Ornstein (1964) and Davis (1964) uses a large

pore stacking gel with minimal sieving effects, between the sample well and the resolving gel (Fig. 3). Both gels and the sample buffers contain chloride ions, while the electrode buffer contains glycinate ions. The pH of the sample and stacking gel buffer is 6.7 while the pH of the resolving gel and electrode buffer is 8.9.

Glycinate is not dissociated at pH 6.7, while chloride is highly dissociated. In an electric field, chloride ions migrate rapidly, moving away from the glycinate ions, leaving behind a solution with fewer ions and hence low conductivity. The low conductivity causes the field strength to increase and a steeper voltage gradient is established in this region. Proteins have a lower mobilty than chloride ions, and will trail behind them at pH 6.7. In the stronger fields, proteins are accelerated and position themselves immediately behind the chloride ions. In the absence of a sieving effect in this low pore gel, proteins are concentrated into a thin layer. When the migrating front reaches the separating gel, the proteins in the sample encounter a smaller pore size and a different pH. At this pH, 8.9, glycinate is dissociated and its mobility is similar to that of chloride ions, and they both accelerate away from the proteins. Proteins will now separate according to their size and charge.

Electrophoresis under denaturing conditions

For proteins in the sample that are poorly soluble or form multimeric aggregates, or for polypeptides that are subunits of a larger structure, the electroseparation needs to be performed in the presence of additives which increase solubility and disrupt aggregates. Protein aggregates are stabilized by hydrophobic interactions and H bonds. The structure of proteins formed by subunits is maintained through disulfide bonds. These interactions need to be disrupted in order to obtain good quality separations. Detergents are used in order to break hydrophobic interactions involved in protein–protein and protein–lipid interactions and increase solubility: SDS (2%) and NP-40 (0.05–1%) are the most commonly used. To break the hydrogen bonds involved in aggregates, urea (7 M) is the most common additive for unfolding proteins. Disulfide bonds between polypeptides can be disrupted with reducing agents such as 2-mercaptoethanol (100 mM) or dithiothreitol (20 mM). Low concentrations of a reducing agent can be added to the buffer in the anode reservoir to maintain reducing conditions during the run. To improve the efficiency of these denaturing agents samples are boiled for up to 5 minutes; however, urea can form cyanate ions which interact with amino groups of proteins (carbamylation). This could result in anomalous separation profiles. Cyanate formation increases with temperature so urea should be added to the samples after heating.

SDS-PAGE

Most proteins can bind up to 1.4 g of sodium dodecyl sulfate (SDS; CH_3-(CH_2)11-O-SO_3- Na^+) per gram of protein.

The saturation of proteins with the negatively charged compound masks the protein's charge, so that the net charge per unit mass becomes constant and due only to the negative charge of SDS. As a result of this, all proteins will move in the same direction in an electric field; the separation will depend entirely on the relative molecular mass and occurs solely as a result of sieving through the pores of the gel.

Conjugated proteins like lipo- and glyco-proteins cannot be saturated effectively with SDS because the carbohydrates and lipids in their side chains do not react with it. This causes bands to be less sharp and could give erroneous results with respect to their molecular weight. SDS and disulfide bond-reducing agents used together dissociate most proteins into single polypeptide chains.

Running conditions

The ionic strength of the buffer and the power applied determine the amount of heat generated during the run. Excessive heat generation increases the rates of diffusion, which will make the bands diffuse. High ionic buffer strength leads to sharper bands but the conductivity is higher and so is the amount of heat generated; the choice of buffer composition must represent a compromise. In a discontinuous buffer system, the resistance of the system decreases during the run, given that the relations between the parameters are:

$H = V\,I/4.185$

$R = V/I$

where H is Joule heating (cal s^{-1}), R is resistance (Ω), V is voltage (V) and I is current (amperes).

At a constant current, voltage and heat will increase with time. At a constant voltage, current drops and heating is reduced. It is recommended therefore that the run is carried out at constant voltage to minimise diffusion. The choice of voltage is a compromise between heat generated by the electrical energy and time required for the run, as a long run time will result in increased diffusion. The running conditions must be adjusted according to the surface and thickness of the gel. Standard conditions are recommended by the equipment manufacturers. All commercially available equipment includes some type of cooling system.

A practical description of the complete procedure to run SDS-PAGE is beyond the scope of this article. A very useful description of the methodology and equipment can be found in technical manuals of the companies that sell products for protein electrophoresis, such as GE Life Sciences.

In the next article of this series, the preparation of samples for protein electrophoresis wil be discussed.

Patricia Leoni
Imperial College London

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Struggling for breath: latest advances in medical research for asthma patients and their families

The British Science Festival 2010, Birmingham, 15 September

Organised by The Physiological Society, Society of Biology and Asthma UK

The Festival saw a week-long celebration of science through talks and practical demonstrations. These were coordinated by national organisations on a variety of scientific topics but few quite as dramatic as *Struggling For Breath*, a talk organised by The Physiological Society focusing on asthma. This comprehensive talk gave me and other attendees a lucid insight into the prevalence of the condition with approximately four children admitted as emergencies every hour. It also focused on the issues surrounding its diagnosis, in addition to current research into a promising new form of treatment. Elizabeth Bell of The Physiological Society chaired the session.

Chris Corrigan (King's College London) started with an overview of the condition. He described asthma as a variable blockage of our airways, or a hyper-responsiveness (abnormal 'twitchiness') of airways.

Sufferers experience asthma attacks that can be triggered by smoke, perfume, deodorant or even fog. Asthma attacks involve the sudden narrowing of the airways through muscle contractions that crush the airways and reduce the volume of air that can pass through them. The airways can also become inflamed and subject to an increase in mucus production which blocks them. Both of these factors reduce the volume of air that can pass through the airways and cause breathing problems. With so many triggers, asthma sufferers are constantly living in panic with the prospect of suffering an attack and needing medical treatment.

As a condition, asthma does not receive too much press coverage, which is surprising when you learn

that 5.4 million people in the UK suffer from asthma, with 1204 people in the UK dying from asthma in 2008 alone. That is more than three people dying every day of the year. The statistics from Asthma UK show that roughly 75% of emergency admissions were from asthma and nearly 90% of asthma deaths are preventable. Professor Corrigan added that asthma costs the NHS £1 billion each year with one child entering emergency admissions every 17 minutes.

Robin Gore (University of Manchester) was the next speaker at the event and presented a variety of case studies of people who had been misdiagnosed as being asthma sufferers. He used audio clips from which you could hear the different coughs before he went on to analyse them. He made his point clearly – there is no good bedside test for asthma and it is very hard to diagnose the disease correctly.

Post-doctoral researcher Ceri Harrop (University of Manchester) then talked about her research into mucus, which we were informed is an important carbohydrate-rich hydrated gel containing electrolytes, proteins, lipids and different mucins (different 'sugar-coated ropes').

Dr Harrop explained that mucus production takes place in goblet cells which make up part of the epithelial lining in our airways. When excessive mucus is produced (such as with asthma sufferers) mucus 'plugs' can form which restrict the airways and make it more difficult to breath.

Whilst mucus can form plugs which block our airways and restrict breathing, it is also exceptionally useful when not over-produced. It forms our body's first line of defence against pathogens and noxious gases. With this in mind, in treating asthma we do not want to eliminate mucus production in sufferers but instead return it to the levels seen in non-sufferers. Below these mucus-producing goblet cells there is the fibroblast cell layer which produces lots of proteins which help impart structure to our airways.

Research is being done into how the goblet cells are connected to this fibroblast cell layer as there could be 'cross-talk' between the cells which may regulate mucus production.

Using bronchoscopy, brushings and pinch biopsies Dr Harrop has been researching in this area. Both procedures involve inserting tubes through the patient's mouth to take a 'sample' of the asthma sufferer's airway.

The sample, consisting of extracted epithelial cells, was then cultured and found to produce biochemically identical mucus. This mucus layer was then exposed to the fibroblast layer and the mucus produced was then analysed. It was found that there was a decrease in mucus production over time which was the opposite of that found in asthmatics. This suggested that the underlying fibroblast cells can regulate mucus production. The next step is to find the natural regulator of mucus production and then reinsert this into the deficient fibroblast cells in asthma sufferers. This potential

treatment would reduce the overproduction of mucus.

We then heard from an asthma sufferer, Sarah Matthews (linked to Asthma UK), who described how her life is affected by the disease. She described the treatment that she receives in terms of inhalers and nebulisers as well as how she deals with her hospital visits. This rounded off an impressive event which was well-attended and provided a better understanding of the disease and the biology behind it.

Steven Forrest
Royal Holloway University of London

Cystic fibrosis event in Glasgow, 4 September 2010

As well as having a lot of fun at the asthma event at the BSA Science Festival in Birmingham, in September we also ventured north of the border to run an event on cystic fibrosis at the Glasgow Science Centre. Our speakers were: Doug Bovell, David Sheppard, Vicky Cowell, Chris Boyd and Jonathan McCormick, who covered a full spread of views on CF issues from the researcher, clinician and patient perspective. Most notable was the young mum of a CF baby who button-holed our speakers to discuss issues after the event. The event was part of the Glasgow Science Centre's Celebration of Science in Scotland programme.

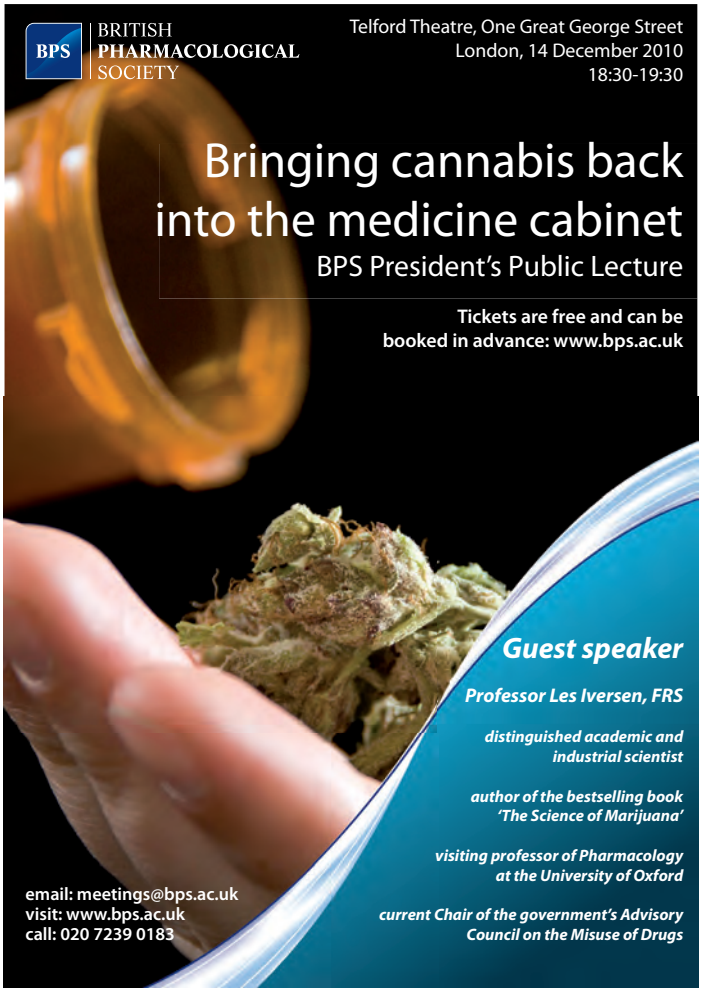
Science is Vital Rally on Saturday 9 October 2010

Evan Harris.

Liz Bell with a new friend, Ben, an economist who works for an investment bank.

We are all very concerned about the possible impact of the imminent Comprehensive Spending Review on science funding. The Society has been working closely with the Campaign for Science and Engineering and the Society of Biology to respond to this, and there has been a very exciting development with the creation of the Science is Vital Campaign. The Society donated £1000 to help them hold a rally outside the Treasury, led by our old friend the former MP Evan Harris. Thousands attended, including me, and the point was well made that scientists aren't prepared to take cuts lying down. The pictures speak for themselves. If you haven't yet got involved with the campaign you can find more information at http://scienceisvital.org.uk/

Liz Bell



100 years ago

The action of atropine, pilocarpine and physostigmine

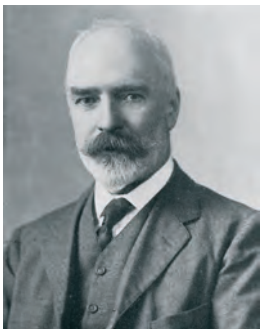
Arthur R. Cushny (1910)

J Physiol 1910 November 9; **41**, 233–245.

Arthur Robertson Cushny (1866–1926) is remembered as the greatest of the early British pharmacologists. However, as there were no specialist journals of pharmacology at the time, much of his published work appeared in *The Journal of Physiology*. The present paper comes from the middle phase of Cushny's career, the thirteen years he spent as the first Professor of Pharmacology at University College London. It records the contractile activity of both pregnant and non-pregnant uterus in anaesthetised cats, and analyses responses to drug injections into the animal.

A theme that ran all through Cushny's career was his interest in the actions of natural products, particularly alkaloids. The 1910 paper employs several. The three in the title are a muscarinic cholinergic antagonist (atropine, from deadly nightshade or *Belladonna*), the muscarinic agonist pilocarpine from a tropical American shrub, and the cholinesterase inhibitor physostigmine (eserine) from the calabar bean. Also used in the paper are nicotine, ergotoxine (a preparation of ergot alkaloids), and the non-alkaloid adrenaline. It is fascinating to note that all six substances are still in use in medicine a full century later.

Cushny's study could be labelled as any of 'pharmacology', 'endocrinology' or 'reproductive biology', which serves once again to emphasise the central position of physiology. The study is also notable in its suggestion of differences in the physiological responses of uteri from pregnant and non-pregnant animals to some agents (pilocarpine) but not others (physostigmine). Cushny also comments at various points on something that has continued to tax researchers studying the uterus to the present day – the variability of the contractile response to different agents. For instance, adenaline causes contraction in some of Cushny's experiments, and relaxation in others. Nowadays we might rationalise this in terms of variable expression of α-adrenoceptors (raising $[Ca^{2+}]$ and promoting contraction) and β-adrenoceptors (raising cAMP and promoting relaxation) in the uterus. Though the problems of understanding uterine contraction and regulation remain, the overall *outline* of the



resolution is now clear, namely the gradual, but ultimately extensive, remodelling of uterine tissue through pregnancy. This includes the remodelling of physiological responses via changes to both receptors and intracellular signalling pathways.

Cushny employs nerve stimulation in several experiments, with complex results; this will stimulate both parasympathetic (cholinergic + nitrergic) and sympathetic (noradrenergic) nerve supplies to the uterus, so it is unsurprising the contractile effects are unpredictable. In 1910 ideas on how nerves stimulated actions like muscle contraction were still forming, with the concepts of chemical transmission in their infancy and a clear understanding of receptors many decades away. Given the complexity of the experimental responses, it is a tribute to Cushny's analytical clear-sightedness that he is able to draw any firm conclusions. He correctly identifies atropine as antagonizing the pilocarpine (muscarinic cholinergic) response in the uterus:

"Pilocarpine differs from adrenaline in being antagonised completely by atropine whether it contracts or inhibits the uterus, while the effects of adrenaline or of [nerve] stimulation are not changed in any way by atropine."

And he comments on where the actions probably occur, suggesting that: "pilocarpine and atropine act on receptive substances which are associated with the nerve impulse path to the uterus, but do not actually lie on this path."

This prescient sentence implies pilocarpine and atropine are not actually on the nerves, but are on the 'pathway' from nerve to uterine contraction – they act, as we now know, on muscarinic receptors on the uterine muscle cells. 'Receptive substances' is the early 20th century concept, due to J.N. Langley, that led in turn to the idea of receptors.

Arthur Cushny, the fourth son of a Scottish clergyman, was born near the cathedral city of Elgin in Moray and studied science and then medicine at the University of Aberdeen. Cushny had already decided to become a professional pharmacologist when he finished his medical degree in 1889; like many scientists of the era he travelled to the German-speaking laboratories to learn the trade of research. He studied in Berne and briefly in Würzburg before settling for several years in Strasbourg as assistant to Professor Oswald Schmiedeberg, often regarded as the founder of modern pharmacology. In 1893 Cushny became Professor of Pharmacology at the University of Michigan in Ann Arbor, where he did pioneering work on the action of digitalis on the mammalian heart and wrote the first notable pharmacology textbook in English. Cushny's *Text-Book of Pharmacology and Therapeutics* – subtitled 'The action of drugs in health and disease' – rapidly became a global standard, going through many subsequent editions and remaining in print after his death.

In 1905 Cushny accepted the chair at UCL and returned to the UK, settiing up a department from scratch. The following year he was elected FRS. Cushny's research at UCL ranged over many areas, including uterine contractility. It concentrated, however, on the two projects for which he is perhaps most remembered: the relationship between optical isomerism and pharmacological action, and the mechanism of urine production by the kidney.

Throughout his career Cushny had sought practical applications for pharmacology in medicine, and in 1918 he relocated from UCL to a Chair in Edinburgh, partly to seek closer collaborations with the clinical pharmacists. Here he remained active in research until his sudden death, from a stroke or heart attack, at the age of 60 in 1926. In his obituary of Cushny, Henry Dale indicates that Cushny had been "aware of a danger threatening his life" for some years since discovering, whilst measuring his own blood pressure in a practical class, that he had hypertension. Given the modern prominence of drug treatments for high blood pressure, and Cushny's life's work, there is a certain sad irony in the relative lack of treatments then available. Dale adds "When the end came it was sudden, as [Cushny] would have wished, and free from the lingering disability which had been his only fear."

Austin Elliott

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Professional paranoia in uncertain times

As a neuroscientist and therefore being of sound mind and neural architecture, I do not under any circumstances suffer from anxiety or paranoia.

But I have with increasing monotony closely observed my scientific colleagues and wondered: Which one of you devious narcissists is plotting to ruin my career? And I have observed that English spiders are increasing in size. I am convinced that some of these spiders are foreign and are therefore swarthy, untrustworthy and venomous. One day a foreign spider will bite my arm which will immediately wither, turn black and require amputation.

I have wondered why I would start to obsess about the size and Machiavellian intent of potentially foreign spiders or the not so common English scientist. I think the real reason is that I am about to be made redundant and when I look around my department I realise that in the next three years up to 25% of us are going to end up – well, anywhere but in science. I don't know really who to blame – our banks I suppose were crooked, our ruling classes deranged, and I suspect that the British government minister responsible for science, Dr Vince Cable gets his profound insights into the construction of an effective British science policy for the 21st century by examining the patterns produced by throwing chicken entrails on the floor. Vince has told scientists that we "must pay our way", should abandon work that is "neither commercially useful nor theoretically outstanding", and finally we also need to "screen out mediocrity".

That last statement really caused me great offence. I am as mediocre as the next scientist! What's wrong with mediocrity, it's my human right to be mediocre, I dream of winning the Nobel Prize for mediocrity. To be lauded as being the most mediocre scientist in my field would be an honour, but the competition would be really fierce as all my peers are really mediocre too.

I also think that the British government is trying to drive me insane and they are using a method pioneered by the CIA in the 1970s. They are trying to damage my brain by asking me to fill out job application forms that have been designed by extremely well-paid consultant surrealists. One recent application form for a lectureship post asked me to provide "evidence of visionary leadership". What is visionary leadership? How can you prove you are a visionary? I mentioned that I had a vision once! The doctor said something about "schizoaffective disorder". I didn't think that would look very good on my CV so I decided to drop the subject. Finally I thought the reference to "visions" might be an oblique suggestion that taking mescaline before a job interview would provide me with the killer competitive advantage, but the only source of mescaline I have is a small cactus I brought last year (*Lophophora williamsii*, £2.35 in a British garden centre, the pink flowers are really nice). Another asked me to provide evidence that I could work in a "dynamic and rapidly shifting customer focused environment" (I won't mention who produced this one). I had to fill out a special form that was designed to eliminate "discrimination". Discrimination on the grounds of suitability for the advertised post I surmised later! I did have one serious problem on this special and no doubt expensively designed form. Immediately following the box posing the psychologically probing question "explain how you felt at a critical phase in your professional life when you exceeded your initial expectations" there was one really totally discriminatory, superfluous and offensive question. "Can you please provide a list of your scientific publications". I then tried to insert my twenty scientific publications into a small box around 2 centimetres high – at this point the electronic form removed 19 of them. After repeated attempts at this I phoned Human Resources and said "I know I am not allowed to send you my CV but can I send you a copy of my publications as an appendix". Human Resources were really helpful "We have made our position clear – this is a form that we have designed to eliminate any possibility of discrimination or unfairness, we do not accept CVs or supplementary material" they explained. "But where do I put a list of my scientific publications?" I said. "That isn't really a constructive attitude, is it?" I was told.

Why? Are employers interested in my sex life? On one equal opportunities form there was a request for me to define my sexual orientation; after male heterosexual, male homosexual and male bisexual there was another sinister box – 'Other – Please specify'. This made me really paranoid as in 1986 I did have a brief drunken flirtation with a sheep called Reg. Is there surviving CCTV footage, does my potential employer really know? Will it affect my future employment? Eventually in case my employers thought me odd I wrote 'Asexual'.

But when I wrote this the spiders in the garden seemed to get much bigger.

Dr Keith Cormorant

Physiology News

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

We are always looking for interesting features, meeting reports, news items and photographs. Contact us (magazine@physoc.org) with your suggestions.

Mobile Teaching Unit sponsorship

For 2010, 2011 and 2012, The Physiological Society has committed sponsorship to the Mobile Teaching Unit (MTU), which is managed by the AIMS CETL (Applied and Integrated Medical Sciences Centre for Excellence in Teaching and Learning) within the University of Bristol. The MTU has proven to be a highly successful resource for raising the profile of physiology within schools and amongst the general public.

The MTU is a lorry that expands into an interactive learning centre, which delivers informal, hands-on physiology teaching sessions to students from the top primary class to A Level. Students have the opportunity to use a range of clinical equipment to take physiological measurements (mainly in the cardiovascular, respiratory and nervous systems) and talk to physiologists about careers in physiology. Teaching materials on body structure and function, including anatomical models and posters, are displayed and sessions can be integrated with PowerPoint presentations. Activities are designed to enrich current topics based on human physiology in the curriculum and can be tailored to the audience.

A one-day visit can accommodate up to 150 students in groups of about 20 for 40–60 minutes each. Sessions are run by University of Bristol and AIMS CETL staff, and sometimes supported by local Physiological Society Members. For more information about the MTU, please visit the AIMS section of the University of Bristol's website at www.bristol.ac.uk.

From 2010 to 2012, The Society will be arranging a number of visits of the MTU to schools and science festivals in Britain. At festivals, the MTU can be used as a drop-in facility with activity stations situated around the lorry. Earlier this year, The Society provided funding for the MTU to attend the Big Bang Fair in Manchester.

The MTU visited Tiffin School on 22 June 2010.

School visits will occasionally be offered as a competition prize for our school/college contacts. We ran three competitions offering the MTU as a prize in 2010: the first winner was Tiffin School in Surrey, who provided the following feedback:

"*On behalf of the school, I would like to thank you very much for arranging the [Mobile Teaching Unit] to come to Tiffin on Tuesday 22 June. It was a tremendous success and both the staff and students gained a great deal from the work they did with the team during the day. The scheme is excellent... and we will certainly encourage other schools to take up the opportunity you so generously gave to us.*"

Hilda Clark

Headteacher, Tiffin School, Surrey

For more information about our school competitions, please visit www.physoc.org/competitions.

The lorry expands into a seminar room, which houses informal physiology teaching sessions supported by presentations, posters and models.

Outreach activity at The Physiological Society

The Society encourages Members to organise outreach activities with funding support from our Outreach Grant scheme. In 2010, we received a significant increase in applications and we would like to thank all those who have engaged in outreach on behalf of The Society; we look forward to building on this success in future years. The following section summarises some reports from the outreach providers; full reports can be found on our website at www.physoc.org/schools

Outreach Grants

The Outreach Grant scheme is open to all Ordinary Members, Affiliates and Associates of The Society who would like to communicate the excitement of physiology to young scientists and the wider community. For more information, please visit our website at www.physoc.org/grants or email grants@physoc.org.

National Science and Engineering Weeks (NSEW) 2011

We are currently accepting Outreach Grant applications from Members who would like to organise an event during NSEW, 11–20 March 2011. The final deadline for applications is 31 January 2011.

Cambridge Hands-On Science summer roadshow 2010

From 28 June to 25 July, Cambridge Hands-On Science (better known as CHaOS) toured Southern and Eastern England with a mission to make science more accessible to students and the general public. CHaOS is a non-profit voluntary group based at the University of Cambridge.

In the 2010 roadshow, the group delivered events to eleven schools (mostly for students aged 9 to 13) and eight public venues, reaching an estimated 4000 members of the public.

Some of the CHaOS team.

Students meet 'Boris' to learn about radiographs.

Using fun, hands-on experiments, demonstrators guided small groups of students through a particular aspect of science, ranging from a large wooden model of the hand showing how antagonistic muscle groups work to genetics by means of extracting and precipitating DNA from kiwi fruit.

Many students appeared to gain a great deal of understanding from the interactive nature of our displays – as well as enjoy themselves too. The feedback we receive makes the effort to organise the roadshow all the more worthwhile – well illustrated by a quote from one student: "the best thing I've ever done in science!"

We are committed to educational outreach and thus keep entrance to our public events free. Although schools are asked for a small contribution to our costs, we rely upon sponsorship for the majority of funding. Careful budgeting and route planning ensures a cost of around £3 per visitor. CHaOS is very grateful for the Outreach Grant awarded to us by The Physiological Society as well as for assistance with the promotion of our events – no doubt many of the enthralled students will be submitting their 'Ask a Physiologist!' forms soon.

If you would like to learn more about CHaOS, please visit our website at www.chaosscience.org.uk, where a more detailed tour report can be found and contact details if you would be interested in having a visit from us as part of next year's roadshow.

Jonathon Holland

Sport and Exercise Physiology Outreach at Nottingham Trent University

Eastwood Comprehensive School was welcomed to Nottingham Trent University (NTU) Sport Science Department to engage in a day of Sport and Exercise Physiology Master Classes. The first session involved the students measuring their own lung and respiratory function (including forced vital capacity and forced expiratory volume), and comparing this with normative data for the general population and athletes. The students discussed the implications of these measurements for both long-term health and sports performance.

The students then engaged in a submaximal exercise test that is used by health professionals to estimate maximal oxygen uptake. The students measured their heart rate response and oxygen uptake, and used this to estimate maximal oxygen uptake. The strengths and weaknesses of the estimation technique were evaluated, with the students providing very insightful comments.

Just prior to lunch, the students experienced the state-of-the-art British Olympic Association accredited environmental chamber, which can be used to manipulate altitude, temperature and humidity. A chilling experience was had by all.

Students use GPS units (situated between the shoulders) to measure their speed and distance during a football match.

Students from Eastwood Comprehensive School with PhD student volunteers at the NTU Sport Science Department.

In the afternoon, global positioning satellite (GPS) was used to measure speeds, distances and forces whilst playing a football match. This technology has just been introduced by several elite clubs from different sports to precisely monitor training loads and match demands. This gave the students a real insight into their own performance and how it compares with elite football players.

Students were also given an insight into University life, and a tour of the facilities and campus.

The day introduced sport and exercise physiology, and provided the students with knowledge about the importance of physiology in both clinical and performance settings. The outreach event was enjoyed by the students (and teacher) from Eastwood Comprehensive, as well as increasing their interest in pursuing science at A2 Level and beyond. Of equal importance was our (staff and PhD students) enjoyment of the day and we have now made a link with the school; we are already arranging future outreach events. One student stated "Loved the day, hope to go again soon"; similarly, we can't wait to welcome them back.

Caroline Sunderland

‘An appetite for science?’ at Imperial College London

In July 2010, the Section of Investigative Medicine at Imperial College London held an outreach event entitled ‘An Appetite for Science?’ Twenty-one 16–17-year-old students from across the UK took part in this fun and educational day, which was aimed at promoting accessibility to higher education, academia and science – and we believe there is nothing more accessible than the science of eating!

The day was run by a mix of scientists at different stages in their careers: academics, postdocs and PhD students with either basic science or medical backgrounds, providing the students with a range of perspectives about working in research. The use of informal lecture-style presentations, hands-on laboratory practicals, topical debates and group work allowed the students first-hand experience of what might await them at university.

A student gets to grips with a pipette whilst performing an experiment to look for the hunger hormone ‘ghrelin’.

The students who attended ‘An Appetite for Science?’.

We started the day with an introductory lecture on the obesity epidemic before students were introduced to the science of appetite control. In small groups, students then learned about the benefits and pit-falls of the body mass index (BMI) by placing their favourite celebrities and sports stars in underweight, normal, overweight and obese categories. This prompted lots of discussion between the students as did the lively debate on the use of animals in scientific research that followed. After lunch, the students conducted a real laboratory experiment and quantified the levels of the ‘hunger hormone ghrelin’ in ‘plasma’ samples, which offered a fantastic opportunity for the students to bring together what they learnt from the lectures into practice in the lab.

Students also learnt about cutting-edge translational research – moving from lab-based *in vivo* studies through to studies in human volunteers. As part of this, the students undertook an activity to design a clinical trial for a hormone identified to have a role in appetite control. The day finished with a lecture from our resident bariatric surgeon. The students learned why the physiological changes in the gut following gastric by-pass surgery currently make it the most successful treatment option for obesity. The students particularly loved the accompanying gory videos of the surgery.

The feedback received from the students was excellent: a report by Sabrina, one of the students who attended the day, can also be found online:

www2.imperial.ac.uk/blog/reporter/2010/08/12/an-appetite-for-science/

We would like to thank The Physiological Society for their continued support of our outreach work, without whom we would be unable to hold this successful and rewarding day.

Michelle Sleeth

Metabolic Physiology Outreach at the University of Nottingham

On 9 July, the Metabolic Physiology group of the School of Biomedical Sciences at The University of Nottingham hosted an enthusiastic group of AS-level students keen to learn more about Human Physiology. We opened our labs to students from The Beckett School and Eastwood Comprehensive, allowing them a first-hand glimpse of what it is like to conduct research into Human Physiology in a university setting.

Students receiving guidance on how to measure blood pressure from Professor Ian Macdonald.

The Metabolic Physiology group is home to a collection of scientists who share a common interest in the regulation of metabolism during health and disease in humans (www.nottingham.ac.uk/BioMedSci/world-leading-research/metabolic-physiology.aspx). With help from postgraduate students along with postdoctoral and academic members of staff, we arranged for the students to undertake several activities within our laboratory, exploring different aspects of cardiovascular, respiratory and muscle physiology. The overall aim of the day was to allow students to see that it is possible to perform integrated physiological investigations in humans. We also aimed to give them an appreciation that human physiology can also be dovetailed with modern molecular biological approaches.

As the day progressed, pre-conceived notions held by students of science being impenetrable, unfashionable or boring disappeared. The students also appreciated receiving hands-on experience of how to take common measurements such as blood pressure, as they were taken through the physiological principles underpinning these important techniques.

Overall, the day was a great success and we had as much fun engaging with the students as they did undertaking the activities. We are indebted to The Physiological Society for both the financial support and guidance that they provided in aid of the event. While the outreach event involved a lot of work, we would highly recommend engaging with local schools as we found the day immensely rewarding.

Andrew Murton

Young Physiologists' Symposium – Neuromodulation

25–26 August 2010
University of St Andrews

This short symposium was held at the University of St Andrews, Scotland's oldest university and shortly to celebrate its 600th anniversary.

Almost a hundred years ago, the celebrated Scottish physiologist and mountaineer T. Graham Brown published his paper 'The intrinsic factors in the act of progression in the mammal'. With the upcoming centenary of this seminal and defining work, and to celebrate the achievements of six centuries of research at St Andrews, young physiologists at the university identified the need to build a network of like-minded early-career researchers in a relevant physiological context.

The theme of Neuromodulation was chosen as it was felt that this best represented a specialism of St Andrews in the wider field of Cellular & Integrative Neuroscience. Neurophysiology at the university is particularly focused on motor control and so in hosting this symposium we wanted to attract delegates from both within our area of expertise and from other areas of neuroscience.

The symposium offered an informal but professional setting and research, both published and ongoing, was presented by a good mix of postgraduate doctoral students, postdoctoral researchers, and invited speakers who included George Richerson (University of Iowa), Ole Kiehn (Karolinska Institutet), Jeremy

Lambert (University of Dundee) and Keith Sillar (University of St Andrews).

A wide breadth of posters were displayed and talk highlights included: Retinoic acid synthesis in astrocytes, Glycine and GABA receptor function in the higher centres of the CNS and Modulation of short-term plasticity of motor cortex via GABAergic disinhibition by non-invasive sensory depravation.

Sheena Tiong (University of Glasgow) won Overall Prize for Best Poster for 'A combined anatomical and electrophysiological study of lamina II interneurons in the rat spinal dorsal horn' and Noboru Iwagaki (University of St Andrews) won the Best Talk for his presentation titled 'Modulation of spinal locomotor networks and motoneuron activity by group I mGluR activation'.

The symposium dinner and ceilidh ensured that there were more chances to network as well as have a great time and a local record may have been set for the most physiologists in a room to 'strip the willow'.

The team behind the symposium was a small but dedicated and enthusiastic group of young researchers, and although this was a steep learning curve in terms of the organisation, project management and external liaison required (everything from the catering, the equipment and room hire, to the travel arrangements, prizes and budgeting), this was an extremely worthwhile exercise in team work, team building and forging lasting connections with other young researchers. All of us involved in planning and running this event hope that we will continue to build on the networks we made as we progress through our future careers.

We would like to acknowledge the generous investment in our personal development made by the GradSkills team at the University of St Andrews, and we also thank our sponsors, Digitimer.

Above all, this symposium would not have been possible without the generous financial, directional and moral support of The Physiological Society.

Catherine Dunford

New Chief Executive appointed by The Society

I am delighted to have been chosen as the new Chief Executive of The Physiological Society by the President and Executive. Without doubt I have inherited a great team of staff from Mike Collis and with my feet newly under the desk, they are already helping me to settle in.

I have known a number of the staff at The Society through a previous role at the Association of the British Pharmaceutical Industry (ABPI) where we worked on key policy issues affecting the life and biomedical research base in the UK, especially in relation to *in vivo* sciences, education and research policy. During these encounters I built a great respect for Mike and his team.

The next few months are going to be a steep learning curve for me, set against a backdrop of a serious threat to science funding and higher education – with the Coalition considering removing the upper limit on tuition fees and increasing the student loan interest rate significantly. This poses a real threat to resource-intensive science education as well as the UK research base. It is critical that The Physiological Society makes the views of its Members known to Government and works to sustain research and education funding.

Consequently, apart from getting to know the staff, Council and meeting as many of the wider membership as I can, my key priorities for the year are to: raise the profile of physiology in Government and Parliament; sustain investment in education from schools to Higher Education; and sustain our research capability. All these will have an impact on the environment and long-term sustainability of physiology in the UK. In order to achieve these, it is critical we work closely with other like-minded learned societies and organisations especially the Academy of Medical Science, the British Pharmacological Society and also the new Society of Biology, but this cannot mean that the voice of physiology is not heard.

Philip Wright

I believe that despite the tight fiscal environment in which the UK finds itself, we have good reason to be optimistic. The Society itself is in a strong position and we have a real opportunity to significantly increase our external impact. Our themed meeting on 'The biomedical basis of elite performance' in the run-up to the Olympic games and the hosting of the IUPS Congress in 2013 both provide opportunities for The Society in the longer term. In the shorter term I will use the networks and contacts in Parliament and Government to ensure the voice of The Society is heard.

Over the next few months I want to meet all the committees whose members play a critical role by providing guidance and contributing their time and energy. I also hope to meet as many of you as possible, by attending some of the scientific meetings and other events The Society organises. However, I do hope that if you have any questions, suggestions or ideas, you will not hesitate to get in touch.

Philip Wright

Philip has over 16 years' experience of the pharmaceutical, biological and biomedical sectors, with a particular focus on strategy, regulation and external scientific affairs.

Ask a physiologist!

Is it true that girls have more taste buds than boys? If so, why? (Josh, age 11)

Professor Tim Jacob, University of Cardiff, replies:

Some people are 'supertasters' some are 'regular tasters' and others are 'non-tasters' based on their ability to taste specific bitter substances (the chemical name of one of them is *n*-propyl thiouracil or n-PROP for short). Some people do not detect these substances at all, while others find them intensely bitter and offensive. About a quarter of people (25%) are supertasters, half (50%) are regular tasters and a quarter are non-tasters. Women are supertasters or non-tasters more frequently, while men tend to be regular tasters – this applies to children as well. The anatomical data also support the gender difference; women do indeed have more fungiform papillae (the little red dots on the front surface of your tongue) and more taste buds. The ability to taste or not taste these bitter substances appears to be determined by genetics. Apparently, if you have a double copy of the gene that confers sensitivity to bitter taste, then you are a supertaster. If you have one copy, you are a regular taster and if you have none, you are a non-taster. The tongues of supertasters are physically different from non¬tasters. Supertasters have more taste buds on their tongue. Consequently, there are more taste buds to send bitter messages to the brain. Our age plays a role in the number of taste buds on our tongue. Children have the most taste buds which may explain why they are more sensitive and tend to be more fussy about what they eat. There is a decrease in taste sensitivity with ageing in women. Only about 7% of women 65 and older were supertasters as compared with the expected 25% in younger women. Supertasters tend to be thin and non-tasters tend to be heavier. Possibly because of the intensity of flavours, supertasters tend to eat less food. Non-tasters, on the other hand, may eat more while searching for a fuller flavour. In evolution, supertasters may have had some advantage since many toxins are bitter in taste. This is particularly important for women since they are responsible for the diet of the baby in the womb and also after birth while the baby is being breast fed. Interestingly, the sensitivity of women to bitterness commonly increases during the first trimester of pregnancy when the fetus is most vulnerable to damage by many toxins. For example, in some women who typically love coffee a strong aversion to coffee's bitterness occurs as soon as they become pregnant.

Why do people hiccup? (Jamie, age 11)

Dr Mary Morrell and Dr Alison McMillan, Imperial College London, reply:

A hiccup occurs as a result of a sudden brief, often violent, involuntary contraction of the diaphragm, and the other muscles used when breathing in. Physiologists have speculated that there could be a 'hiccup-generating centre' leading to stimulation of the phrenic nerve. But neither the centre nor the precise physiological trigger for the hiccup has been identified so far. The 'hic' noise comes when the breath is cut off by the closure of the vocal cords snapping the windpipe shut. The stereotypical sequence of muscle contractions is complex and the hiccup shares some similarities with coughs, sneezes or yawns.

There are many theories as to why we hiccup although no one is really sure. One idea is that hiccups evolved when we walked on four legs, and that they helped us to swallow food stuck in our throats. Now that we walk upright, swallowing is aided by gravity. The sharp breath in creates a vacuum behind the food to help suck the lump down. This might explain why dogs eating food quickly are prone to hiccups. Other suggestions are that hiccups result from our evolution as sea creatures, when gills were used to breath. Finally, they could be linked to how we learn to suck as babies.

Hiccups are extremely common, and are rarely associated with severe diseases. Most cases of hiccups resolve inside a few minutes to an hour, and are known as common hiccups. Persistent hiccups last for up to 48 hours. If they last for more than 2 months they are classed as intractable or diabolic hiccups; these hiccups are usually due to more serious illness or medication. Suffering long-term hiccups can be a problem, since they can cause fatigue, loss of sleep and mental or physical exhaustion.

There are literally hundreds of recommended 'cures' for hiccups: drinking out of the back of a cup, a cold key down the shirt and being frightened are commonly used. Usually the best cure is holding your breath to gain control of your breathing muscles. Several more physiological cures for chronic hiccups exist including stomach distension, digital rectal massage, pulling hard on your tongue. These work by stimulating the vagus nerve.

Hiccups have been around for millions of years and the exact cause remains a mystery.

Get involved and write an article for *Physiology News*

Have you done something in your studies you would like to recommend to other young scientists, attended an amazing training course or got an issue you'd like to get off your chest? If you enjoy writing then why not contribute to *Physiology News*. We have an annual prize of £200 for the best published article written by an Affiliate or young scientist. If that isn't enough incentive, contributing to the magazine is a great extra on your CV and a nice way to tell a broader audience about the things you do. We are always looking for people to contribute to the Affiliate pages in the magazine and would love to hear from anyone who would like to get involved.

Email us for more information or to discuss ideas at magazine@physoc.org

Biochemical Society Conferences

5–7 January 2011
Robinson College, Cambridge, UK

DEADLINES:
Abstract submission 26 OCTOBER 2010
Earlybird registration 3 DECEMBER 2010

The Biochemical Society Annual Symposium

Recent advances in membrane biochemistry

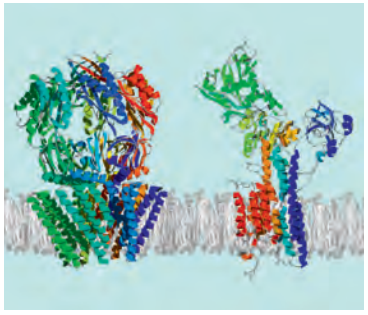

Image kindly supplied by Frank Michelangeli (University of Birmingham, UK)

Organizers:
Frank Michelangeli
Malcolm East

Overview:
This symposium will focus on the latest developments and breakthroughs within the field of membrane protein structure and function. Membrane biology underpins a vast array of life processes such as bioenergetics, signalling and transport.

Topics:
* Membrane protein expression and structural analysis
* Recently elucidated membrane protein structures
* Modelling of membrane protein structure, folding and dynamics
* Lipid-protein interactions
* Membrane proteins in pathology

Biochemical Society Transactions is the only publication to include this major international meeting. It is scheduled to appear in Issue 39(3) and as a stand-alone volume of the online Symposia series.

For a full programme please visit:
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The Journal of Physiology

New Editors 2010

Ian D. Forsythe

Group Leader, Neurotoxicity at the Synaptic Interface, MRC Toxicology Unit, University of Leicester, Leicester LE1 9HN, UK.

I conducted my PhD on *in vitro* spinal cord neurophysiology at the University of Southampton under the supervision of Gerald Kerkut and Jeff Bagust. Maintaining an interest in primary afferent depolarization (PAD) and presynaptic inhibition, I did my first postdoc at the John Curtin School of Medical Research in Canberra, Australia under the supervision of Steve Redman. In 1985 I received a Fogarty Fellowship to work with Phil Nelson and Gary Westbrook at NICHD, National Institutes of Health, Bethesda, MD, where we first demonstrated slow time-course synaptic currents mediated by NMDA receptors at glutamatergic synapses (this was published in *The Journal of Physiology* in 1988). Later in 1988 I returned to the UK to work with Peter Stanfield at the University of Leicester on voltage-gated potassium channels. I received a Wellcome Senior Research Fellowship to develop the auditory brainstem preparation from which in 1994 I first made direct patch clamp recordings from the giant excitatory synaptic terminal called the calyx of Held (also published in *The Journal*). Our studies focused on exploring the mechanisms of transmitter release, calcium channels, synaptic integration and brainstem auditory processing. I joined the Editorial Board of *The Journal of Physiology* between 1995 and 2002 and I was a member of the Wellcome Trust Neuroscience Panel from 2002 to 2005. I was awarded a Chair of Neuroscience in the Department of Cell Physiology and Pharmacology at Leicester in 2000, and in 2005 I moved to join Pierluigi Nicotera in the MRC Toxicology Unit at Leicester. Here I continued our basic studies of synaptic transmission and voltage-gated potassium channels and allied this to applied studies of neurodegeneration using electrophysiological methods. Over the last 5 years we have focused on brainstem damage caused by hyperbilirubinaemia and auditory insult, we have characterised the physiological mechanisms of nitric oxide signalling in the auditory brainstem, and are developing methods to study neuronal ion channel homeostasis and neurodegeneration. A key objective is to understand the different physiological roles of native delayed rectifiers (voltage-gated potassium channels) in neuronal excitability. I have recently joined the Editorial Board of *The Journal of Physiology* as Senior Editor and Reviews Editor.

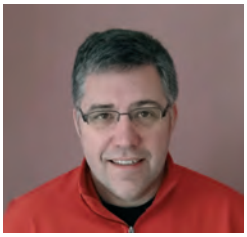
José González-Alonso

José González-Alonso, Professor of Exercise and Cardiovascular Physiology, Brunel University, West London.

José González-Alonso is an integrative human physiologist with particular interest in the regulation of skeletal muscle blood flow and the cardiovascular determinants of exercise performance. His research has contributed importantly to advance our understanding of the circulatory limitations to exercise and the role of erythrocytes and coupled intravascular adenosine triphosphate (ATP) signalling in the control of the human skeletal muscle circulation. His interest on the limits of human performance reflects his devotion to competitive endurance and middle distance running since childhood.

José is an international researcher. He completed his undergraduate studies in Physical Education in Barcelona (Spain), his MA and PhD in Exercise Physiology at the University of Texas at Austin (USA) and his post-doctoral training at the August Krogh Institute, University of Copenhagen. From 1999 to 2005, he worked as a senior researcher at the Copenhagen Muscle Research Centre (CMRC), a world-renown centre of excellence in integrative human physiology directed by Professor Bengt Saltin. In 2006, José joined Brunel University's School of Sport and Education to create and direct the Centre for Sports Medicine and Human Performance.

Paul Greenhaff



Paul Greenhaff is Professor of Muscle Metabolism at the University of Nottingham, where he has worked for nearly 20 years (and which he believes have passed far too quickly)! Paul has specific research interests in the area of skeletal muscle metabolism. Members of his research group possess a range of expertise and skills necessary to perform integrated metabolic investigations in healthy human volunteers and patients, which are dovetailed with relevant animal and molecular biological approaches facilitating a translational approach to research. Current research interests are focused on the control and integration of muscle fuel utilisation in health and disease, and the molecular regulation of muscle mass under a variety of conditions. Particular focus has been directed towards investigating the

impact that exercise, inactivity, and nutritional and pharmacological interventions have in modulating muscle mass, metabolism and function. This is Paul's second stint as a member of the Editorial Board of *The Journal of Physiology* and he is looking forward to the challenge. Over recent years he has also been a member of The Society's Council and currently sits as a non-council member of The Society's Finance Committee.

David Lovinger

David M. Lovinger is a neuroscientist studying the neural basis of action control, habit formation and addiction. Throughout his career he has examined neurophysiological mechanisms that contribute to brain information storage. Current research in his laboratory is focused on molecules involved in modulation and plasticity of synaptic transmission at corticostriatal synapses, with particular attention to long-lasting changes in synaptic transmission (such as long-term potentiation and long-term depression of transmission) thought to contribute to learning and memory. The laboratory is also investigating how molecules involved in striatal synaptic plasticity participate in skill and instrumental learning. Activity of neurons in corticostriatal circuitry during action learning and performance is also a focus of Dr Lovinger's research. The corticostriatal circuitry also participates in the development of addiction. In this context, the laboratory is examining neuropharmacological effects of addictive drugs on striatal synaptic transmission. Effects of long-term exposure to addictive drugs on this circuitry are also being investigated, with an eye to determining what changes in neuronal function and synaptic transmission underlie addiction.

Dr Lovinger received a BA in Psychology from the University of Arizona in 1981 and in 1987 he received his doctorate in Psychology from Northwestern University. At Northwestern, he worked with Dr Aryeh Routtenberg studying the roles of protein kinase C and its substrate, the GAP-43/F1 protein, in hippocampal long-term potentiation. His post-doctoral research at the National Institute on Alcohol Abuse and Alcoholism (NIAAA), National Institutes of Health, focused on the effects of alcohol on ligand-gated ion channels. In 1991 Dr Lovinger moved to the Vanderbilt University School of Medicine as an Assistant Professor in the Department of Molecular Physiology and Biophysics, where in 1998 he rose to the rank of Professor. Dr Lovinger returned to NIAAA in 2002 as a Senior Investigator and Chief of the Laboratory for Integrative Neuroscience.

Gianmaria Maccaferri

Dr Maccaferri received his MD and PhD from the University of Milan, Italy, where he worked with Dario DiFrancesco studying the role of the hyperpolarization-activated current in hippocampal pyramidal cells. He then trained as a post-doctoral fellow with Chris McBain at the National Institutes of Health, Bethesda, Peter Somogyi, at the MRC, Oxford, and Ray Dingledine at Emory University in Atlanta investigating the synaptic properties of specific types of GABAergic interneurons.

In 2002, he joined the faculty at Northwestern University where he currently is Associate Professor at the Department of Physiology. His laboratory studies the anatomical and physiological properties of GABAergic interneurons and Cajal–Retzius cells of the hippocampus, and their role in the regulation of physiological and epileptiform network activity.

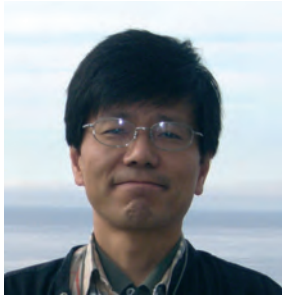
Giovanni Mann

I obtained a BSc in Zoology (1973) from George Washington University, Washington DC, USA and MSc (1974) and PhD in Physiology (1978) from University College London. I am currently Professor of Vascular Physiology in the Cardiovascular Division, School of Medicine at King's College London. In the past I served as Chairman (and Deputy Chairman) of the Executive Committee of The Physiological Society, President of the European Pancreatic Society, and as a Council Member of The Physiological Society, Society for Free Radical Research-Europe, European Society for Microcirculation, Microcirculatory Society USA International Liaison Committee and am currently President of the British Microcirculation Society.

My research and editorial expertise lies in the field of vascular biology and reactive oxygen species. I am currently also an Associate Editor for *Free Radical Biology & Medicine* and on the Editorial Boards of *Microcirculation* and *Free Radical Research* and the International Advisory Board for *Acta Physiologica Sinica*. I currently chair the Translational Sciences Panel of Heart Research UK, and am on the Board of External Referees for the BBSRC and College of Experts for the MRC – Physiological Systems & Clinical Sciences, and previously served on grant panels of the British Heart Foundation and Guy's

Charitable Foundation. At King's College London I am closely involved in postgraduate studies and as Head of Graduate Research in the School of Biomedical Sciences. Throughout my career in the UK at UCL, Queen Elizabeth College and King's College, I maintained a strong link with physiology, supported *The Journal* both as an author and reviewer, and hope to facilitate the submission of vascular biology and redox signalling papers to *The Journal*.

Yasushi Okamura



I am currently the professor of the Department of Physiology, Graduate School of Medicine, and Graduate School of Frontier Biosciences at Osaka University. The physiology course has more than 100 undergraduate students every year. We decided to start teaching individual students the two-electrode voltage clamp technique of *Xenopus* oocyte as well as classical teachings such as electromyograms. Our group has been studying ion channel molecules and voltage-sensing phosphatase by integrating electrophysiology, structural biology, enzyme chemistry and mouse gentics. I started my career working on developmental changes of membrane excitabilities during the ontogeny of tunicate, a marine invertebrate, under the supervision of Professor Kunitaro Takahashi. I learned molecular biology in the laboratory of Dr Gail Mandel (who is a National Academy member, currently at Vollum Institute) as a postdoc. For many years from my earliest days in science, I have been lucky to work on my own project. Although I am currently working on channel molecules themselves and their functions in mammals, we always pay attention to diversities among species. For two years after I moved to Osaka University, it was necessary to live alone 120 miles away from my family, as is usual for many researchers in Japan. However, since spring of this year, I fortunately live with my family in a town near Kobe city where I spent my high school years. The town is close to both the ocean and mountains. A historical house that was designed by Frank Lloyd Wright is also close to our house. We have fun walking along the river and on the trails in the wood where we sometimes see wild boar.

Stephen Roper

My first opportunity to review for *The Journal of Physiology* was when I was a young American Fulbright Scholar completing a PhD degree in Physiology at the 'Godless Institution of Gower Street', University College London, when AF Huxley was department chairman. My thesis advisor asked me to help him review a manuscript *The Journal* had just sent him. I have held *The Journal* in high esteem ever since and am delighted to join my expert colleagues on the review team. After graduating from UCL, I trained with Stephen Kuffler at Harvard and subsequently joined the faculty at the University of Colorado Medical School. From there I spent some time as chair of the newly named Department of Anatomy and Neurobiology at Colorado State University, then was recruited to the University of Miami School of Medicine where I am a professor in the Department of Physiology & Biophysics. When I'm not in the lab, I'm back in the Colorado mountains skiing or hiking with family and friends, or sea kayaking in warm waters off the Florida coast. I study sensory neurobiology and specifically the chemical senses. My associates and I are interested in the cellular and molecular events that occur in the peripheral sensory organs of taste, and especially the synaptic interactions and signal processing that occur in taste buds during gustatory excitation. We use functional imaging to analyse how taste cells are activated by stimuli and to identify the neurotransmitters released during stimulation. Details are on my website: www.biomed.miami.edu/sroper

Lin Chen

Professor at the Department of Biological Science, Section of Molecular and Computational Biology, University of Southern California, Los Angeles, CA, USA.

Lin Chen (University of Southern California, USA) obtained his PhD degree in the Chemistry department at Harvard University in 1994. He did his postdoctoral training in structural biology in the Department of Molecular and Cellular Biology at Harvard University. His research interests include: (i) mechanisms of eukaryotic gene regulation, including the molecular basis of signal transduction, transcription regulation and epigenetic control of chromosome structure; and (ii) structure and function of nicotinic acetylcholine receptors and other ligand-gated ion channels.

Flemming Dela

Flemming Dela is 53 years old and has an MD from the University of Copenhagen (1989). He obtained his Doctor of Medical Sciences in 1996. After basic clinical training, Flemming has been doing full-time research with the focus on human cardiovascular and metabolic

adaptation to exercise and physical training in health and disease (e.g. diabetes, insulin resistance, heart failure, atherosclerosis, ischaemia). He is currently professor in Physiology at the University of Copenhagen in the Center for Healthy Aging.

Carsten Lundby

In the mid 90s I was still in high school and trained running wearing a snorkel to induce hypoxia and thereby hoping to increase performance – retrospectively this may not have been very smart – but my interest for oxygen transport always seems to have been there. My interest for integrative human physiology as a research topic was initiated when I participated as a subject in a scientific high-altitude expedition to La Paz in Bolivia. During the ten-week-long study, new techniques and principles were introduced almost on a daily basis. The study was led by Professor Bengt Saltin from the Copenhagen Muscle Research Center in Denmark and included many international top researchers. I am not sure if my learning curve has been steeper since then! A few years later I obtained my PhD from this institute, with Bengt Saltin as my supervisor. Since the beginning of my research career my main interest has been oxygen transport and utilization, and how humans adapt to stimuli such as altitude, exercise and pharmacological manipulations. After a postdoctoral period in Switzerland, where I was introduced to work done on transgenic animals overexpressing erythropoietin, I was appointed Assistant Professor at the Department of Sport Science at the University of Aarhus, where I was subsequently also appointed Associated Professor. During this period my work was focused on non-erythropoietic functions of erythropoietin when injected in humans. My current research group at the Zürich Center for Integrative Human Physiology in Switzerland focuses on topics within human physiology such as mitochondrial function in health and disease, regulation of brain blood flow, adaptations to altitude exposure, regulation of cardiac output and blood volumes, and physiological responses to exercise training and bed-rest. Needless to say most of our lab meetings are held while jogging the Zürich hills.

The Journal of Physiology symposium

The Journal of Physiology symposium 'Reactive oxygen and nitrogen species in skeletal muscle: acute and long-term effects' took place on Saturday 11 September in Abano Terme, Italy. It was organized by Roberto Bottinelli and Håkan Westerblad as a satellite symposium preceding the European Muscle Conference 2010. Abano Terme, a slow-paced spa resort close to Padova and Venice, turned out to be an excellent location for the symposium. The seven talks of the symposium were presented in the main lecture hall of the Congress Center Pietro D'Abano and attracted an audience of around 200 people. The format of the symposium giving each speaker a relatively long time (about 30 min presentations followed by 10 min for questions) worked very well and inspiring discussions occurred after each talk. Further discussions took place during the morning and afternoon coffee breaks and the lunch, which could be enjoyed outdoors in perfect late-summer sunshine. A slightly unexpected take home message of the symposium was that muscle disuse, rather than increased muscle usage, is accompanied by problems induced by reactive oxygen–nitrogen species.

The talks from the symposium will be published in *The Journal of Physiology* early in 2011.

Membership Subscriptions for 2011

The Society is pleased to announce that there will be no change to the membership subscriptions for 2011.

Membership Category	Membership Fees 2011	With Direct Debit
Ordinary member	£90	£70
Affiliate	£20	£15
Associate	£45	£35
Undergraduate Associate *Join alone* (single payment)	£15	
Undergraduate Associate *Join as group of members* (single payment)	£10	

The option for Ordinary Members to subscribe to hard copies of The Society's journals has been removed.

For further information, please contact membership@physoc.org

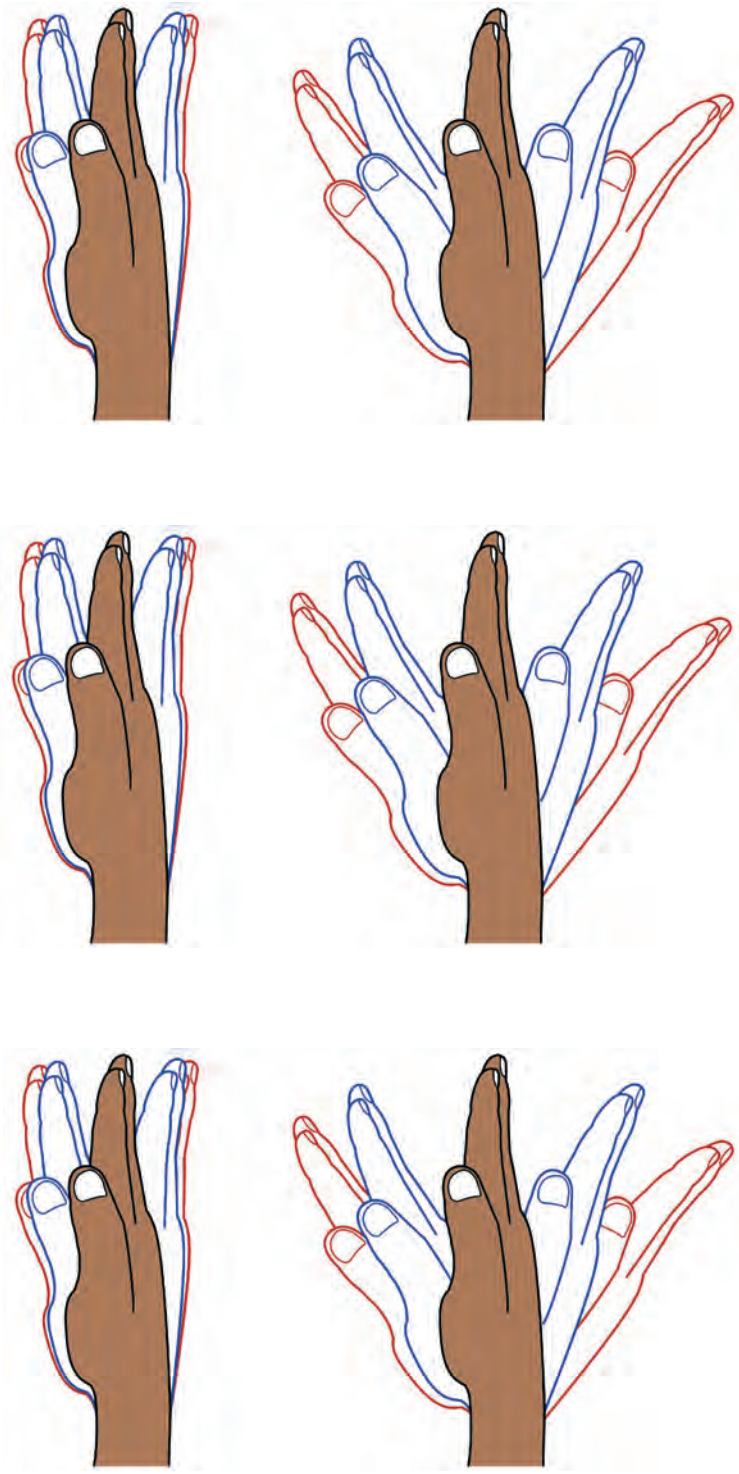
IUPS 2013

21–26 July 2013 Birmingham, UK

www.iups2013.org

37th Congress of the International Union of Physiological Sciences

The International
Convention Centre (ICC)
Birmingham, UK



Phantom hand movement (p. 34).

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