25th anniversary issue

PHYSIOLOGY NEWS

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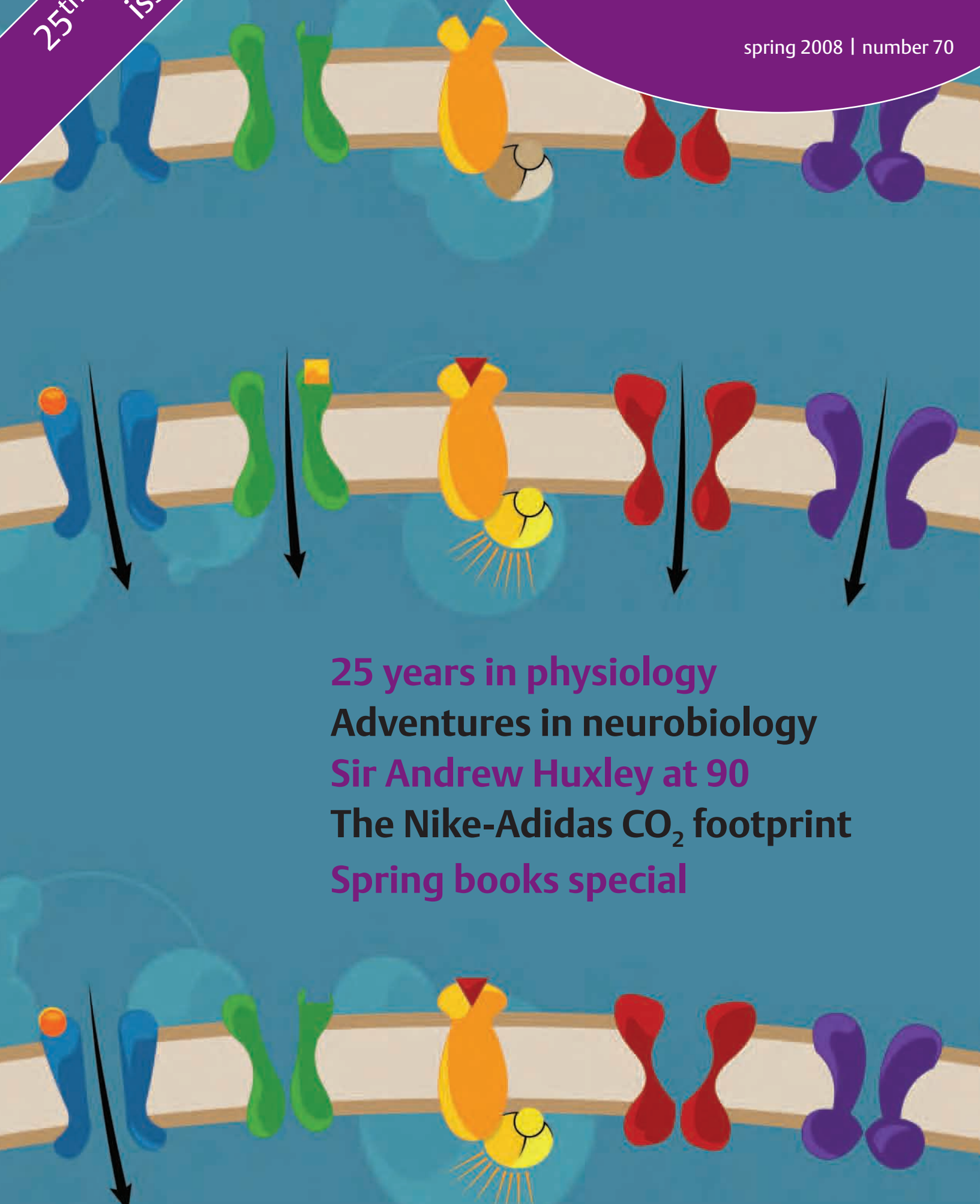


25 years in physiology

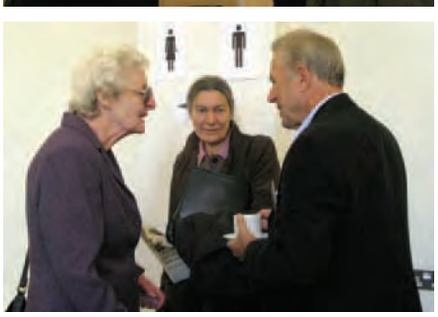
Adventures in neurobiology

Sir Andrew Huxley at 90

The Nike-Adidas CO_2 footprint

Spring books special

International Symposium
in honour of Sir Andrew Huxley
on the occasion of his 90th birthday
14 November 2007
University College London



See also Gerald Elliott's report on the symposium and more images on p. 37 (*photos by Martin Rosenberg and Roger Thomas*).

Sir Andrew Huxley (front, centre) also celebrated his 90th birthday at a Society dinner with Prem Kumar (back, left), Colin Blakemore, Mike Collis, Graham McGeown, Dafydd Walters and Ian McGrath (front, left) and Denis Noble.

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

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Contributions and queries
Senior Publications Executive
Linda Rimmer
The Physiological Society Publications Office
P O Box 502, Cambridge CB1 0AL, UK

Tel: +44 (0)1223 400180
Fax: +44 (0)1223 246858
Email: lrimmer@physoc.org
Web site: http://www.physoc.org

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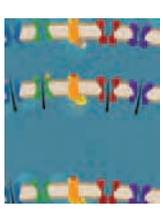

Front cover image from Norton *et al.* (p. 28). Graphics by Jan Kowalczewski.

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Action points

Grants
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Members should inform the Administration Office of any changes of address, telephone, fax or email address. Changes can be emailed to: imagre@physoc.org

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Physiology News

Deadlines

Letters and articles and all other contributions for inclusion in the Summer 2008 issue, No. 71, should reach the Publications Office (lrimmer@physoc.org) by **30 April 2008**. Short news items 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 Senior Publications Executive 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. In particular, scientific articles should give a good overview of a field rather than focus entirely on the authors' own research.

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

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

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

Illustrations and authors' photographs
Authors are encouraged to submit diagrams, drawings, photographs or other artwork with their articles or to suggest appropriate illustrations. A photograph of the author(s) should also accompany submissions, if possible. Illustrations and photographs may be colour or black and white, prints, transparencies or tif/jpeg files with a **minimum resolution of 300 dpi**. Electronic colour figures should be saved in **CMYK mode**.

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

Opinions expressed in articles and letters submitted by, or commissioned from, Members, Affiliates or outside bodies are not necessarily those of The Physiological Society.

In this issue

This issue of *Physiology News* celebrates several anniversaries, and also welcomes some new faces.

The first ever Physiological Society magazine (then the *Newsletter*) appeared in 1983, which makes this our 25th anniversary issue. Since we published a historical retrospective on our 20th anniversary (see PN **54**, 30–32), for our quarter century we have decided to look at how physiology itself has changed in the interim. Physiological Society President Ole Petersen gives a personal view on pages 4–7.

Yet another anniversary is that of *Experimental Physiology*, which is celebrating its centenary – you can read a little about its first ever paper on p. 60, while for more on Its history Society Members can go to the January issue at http://ep.physoc.org/content/vol93/issue1.

We also welcome some new faces to *Physiology News*. Since the rest of the editorial team are, to put it politely, a fair way the wrong side of 30, younger faces were needed, and we are delighted to welcome two of them – Fiona Randall and Rehana Jawadwala, who between them will be covering Affiliate issues (and other things) and hopefully giving us a bit of a fresh perspective (p. 48).

Finally, I have left the most memorable anniversary until the last. In November 2007, Professor Sir Andrew Huxley FRS, Nobel Laureate, celebrated his 90th birthday with a symposium in his honour at UCL. We are delighted to wish him a slightly belated happy birthday, and to salute his magnificent scientific achievements (see p 37–38 and the inside front cover).

Austin Elliott
Editor

Physiology in medical teaching

Basic science knowledge among, and teaching to, UK medical students – and students on other "biomedical" vocational degrees – is back in the news.

Undergraduate medical training in the UK underwent a major shake-up in the mid 1990s, with a major theme being to decrease the amount of 'detail' in medical curricula. In the years since, a number of established medical schools have shifted to more integrated or (most radically) to problem-based learning (PBL) teaching systems, while the new medical schools established since 2000 have also mostly adopted these less traditional methods. Other universities have retained the traditional '2 years basic science, 3 years clinical' model.

Since the mid 1990s there have been ongoing rumblings about 'loss of core knowledge'. PBL takes most of the public flak, with the caricature being of tutorials with tutors who are forbidden to speak, and students acquiring 'communication skills' but bypassing basic grounding in anatomy, physiology and pharmacology. The rumbling has got a bit louder recently, largely as a side-effect of the unease over the disastrous attempt at reform of postgraduate medical training.

It is not my purpose here to debate medical teaching methods, although, for the record, I am an organiser of part of a PBL medical course and the caricature I have just outlined is a long way from the reality as I experience it. I would, though, like to comment on some of the broader issues of university physiology groupings – I hesitate to say 'departments' any more – and medical student teaching.

Where physiologists teach both students doing BSc degrees – including physiology – and students from professional degrees 'owned' by other departments, there is obvious potential for this to default to being seen as teaching 'our' and 'their' students. And as modern curricula for degrees like medicine have diverged from the standard 'yr 1 lecture course in basic physiology' model, the divide has widened. Under these circum-stances, the potential for staff in basic science departments to lose a sense of ownership of the 'service' teaching – including medical teaching – is obvious. And with this loss of ownership comes an inevitable inclination to disengagement.

Why fight for the inclusion of more basic science in the curriculum for some professional degree, if the degree is owned by another departent which seems disinclined to listen?

However, my firm view is that this is too easy a way out. And we have been here before, in some cases, back when the changes to medical degrees were first proposed more than a decade ago. There was a definite strand of opinion within physiology departments then to the effect that, if medicine wanted to teach students by PBL, and to decide what basic science – if any – was in and how they wanted it taught, then we scientists would tell them they were welcome to it – provided they did it all themselves and left us out of it. Physiologists would simply get on with research, and with training BSc and PhD students.

This was perhaps a natural reaction to the high-handedness that many physiologists tell me they detected, and sometimes still detect, in medical curriculum groups. But it was a dangerous road to go down. If there are now medical degrees which don't contain enough physiology – and there is more hot air than evidence on this point – then I would expect to find them in precisely the universities where disengagement of basic scientists from medical teaching is most marked. In which case, the fault does not necessarily lie entirely on one side.

The key to having basic sciences properly incorporated in a medical degree course is surely to have basic scientists as a core part of the group of people designing, running, and delivering the course. If we surrender these responsibilities wholly to medical education specialists and clinicians, then we cannot complain about the results.

In other words, engagement means influence. Most basic scientists think – and I include myself here – that basic scientists know a lot more about teaching underlying physiological concepts to medical students than medical doctors do. And most would worry about curricula where students rarely see a basic scientist outlining and explaining those concepts, whether that is as a lecturer or as a tutor. But this is the kind of point that needs making, forcefully – and even if those there don't seem to want to hear it – from *within* curriculum committees. Not just from a lab a safe distance away.

A short-sighted decision

A few weeks before this issue went to press, *Nature* reported (17 Jan) that the Novartis Foundation (formerly the CIBA Foundation), located in London's Portland Place, was to close its doors[1]. This will have saddened many scientists, including physiologists, who have benefited from the Foundation's activities. The Foundation was established as a scientific meeting house in 1949. Since then it has run more than 400 symposia, typically small-scale 3-day events with 30 or so participants modelled on 'mini-Gordon Conferences', but followed by open meetings to allow a wider audience to hear the speakers.

Novartis has now decided to pull the plug. *Nature* quotes a Novartis spokesman as stating that the meetings 'did not allow [Novartis] to maximize our impact'. Although the Academy of Medical Sciences seems likely to take over the building in Portland Place, without a significant sponsor the symposia seem set to disappear.

In an accompanying editorial[2], *Nature* characterizes Novartis' decision as 'blinkered', while making the point that the Foundation could perhaps have done more, both to modernize in recent years and to campaign publically to try and change Novartis' mind. In an age beset (cursed?) by seemingly endless reorganisations, few scientists would probably argue with *Nature's* comment that 'It is easier to destroy an organization with a strong reputation and institutional knowledge than to build one up from scratch.'

Many Physiological Society Members will have participated in one or other of the Foundation's activities, or even just stayed in the rooms at Portland Place, which have always been available, between conferences, as a (somewhat idiosyncratic) place for scientists to stay in London. In addition, the Foundation's bursary scheme has allowed selected young scientists to attend the 'closed' symposia and then work for a period in the laboratory of one of the symposium participants.

It is sad to contemplate the end of these activities, and of a UK-based tradition of international scientific meetings, and one would therefore hope that a new sponsor for the Foundation's activities can be found. Perhaps if any Physiological Society Member has contacts among the super-rich they might like to have a quiet word?

Austin Elliott

[1] *Nature* **451**, 233 (2008). http://www.nature.com/news/2008/080116/full/451233a.html
[2] *Nature* **451**, 224 (2008). http://www.nature.com/nature/journal/v451/n7176/full/451224a.html

Physiology then (1983) and now (2008)

Ole Petersen looks at the changes in physiology during a quarter of a century of The Society's magazine, and has confidence that the future is in excellent hands

In 1983, when The Physiological Society started publishing its magazine, most medical schools in the UK had a physiology department, there was no national Research Assessment Exercise (RAE), no journal publishing short (trends-like) physiological review articles and most neurophysiologists regarded themselves as physiologists rather than neurobiologists. The first RAE was conducted in 1986 and in that same year *NIPS* (*News in Physiological Sciences* now *Physiology*) was launched by the American Physiological Society (APS) and the International Union of Physiological Sciences (IUPS). The neuroscientists gradually became more inclined to separate themselves from the physiological community, increasingly holding their own meetings and establishing their own journals (*Neuron* was established in 1988). On the other hand, two of the techniques that have dominated major parts of physiological research these past 25 years were invented and already yielding important information before 1983, namely the patch clamp technique (Hamill *et al*. 1981; Verkhratsky *et al*. 2006) and the recording of Ca^{2+} signals with fluorescent probes (Tsien *et al* .1982; Petersen *et al*. 2005).

In this short article it is, of course, impossible to do justice to the general theme concerning how the field of physiology has changed over the past 25 years. I can only do so from the rather narrow perspective of my own experience and work. I nevertheless believe that some points will emerge from even such a limited exercise that may illustrate some of the general trends for the subject.

1983

In 1983 I was only a couple of years into what would turn out to be a long period (17 years) as Head of the Physiology Department at Liverpool University, having succeeded Rod Gregory FRS as George Holt Professor of Physiology in 1981. However, it could easily have become an even longer period, since my contract – in line with the general trend at the time of my appointment – specified that my chair was linked to the headship of the Department and the expectation was that I, like my predecessor, would remain in charge of the Department until my retirement. If I had not succeeded in obtaining an MRC Professorship in 1998, this would probably have been my fate!

Figure 1. Symposium celebrating Rod Gregory's 70th birthday during a meeting of The Physiological Society at Liverpool University in 1984. From left to right, front row: Viktor Mutt, Roger Guillemin, Rod Gregory, Charles Code; back row: John Walsh, Irene Schulz, Ole Petersen, Ken Agarwal, Andrew Soll, Graham Dockray.

In 1981, when I had moved from the University of Dundee – where I had been Head of the Physiology Department for 6 years – to Liverpool, I was the only professor in the Department. One of my first actions in Liverpool had been to make sure that Graham Dockray was promoted to a chair, and this happened in 1982. The whole development of physiology in Liverpool, which led to the Department becoming recognized in every single national RAE as the leading research department in the UK, was forged in a close and interactive collaboration between Graham and me. One visible early sign of this was the successful meeting of The Physiological Society in Liverpool in 1984, at which Graham and I organized a symposium celebrating Rod Gregory's 70th birthday (Fig. 1).

1983 was a good year for my own research. Yoshio Maruyama was my closest collaborator in the laboratory at that time, having arrived from Sendai (where he is now Professor of Physiology) while I was still in Dundee. As described in the written version of the first John Young Memorial Lecture which I delivered at the Gordon Conference on *Salivary glands and exocrine secretion* in California in 2005 (Petersen, 2005), Yoshio (Fig. 2) built our first patch clamp amplifier and recorded the first single channel currents from epithelial cells (Maruyama & Petersen 1982). Soon thereafter we found, to our great surprise, that the salivary gland acinar cells, which do not conduct action potentials, nevertheless possess voltage-gated K^+ channels, namely Ca^{2+}-activated maxi-K^+ channels (Fig. 2). In the *Nature* paper describing these results (Maruyama *et al*. 1983), we

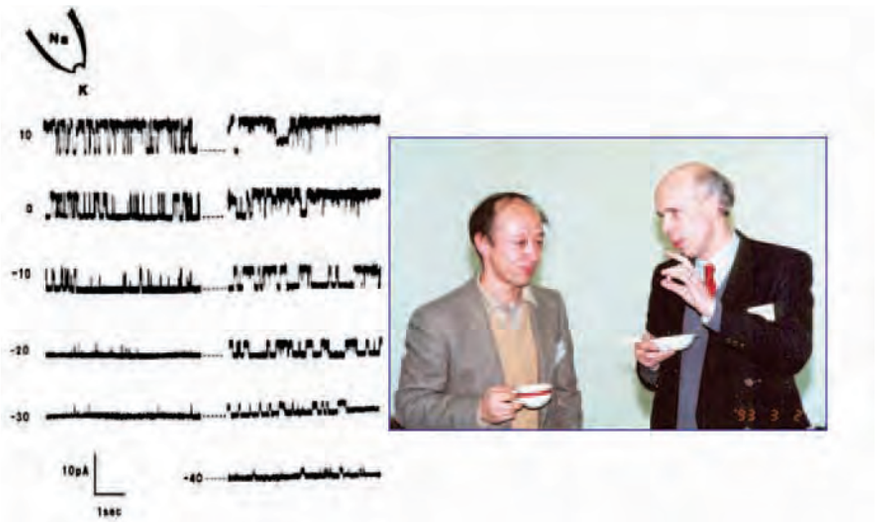

Figure 2. The first demonstration of voltage-activated ion channels in a transporting epithelium. Patch clamp single channel current recording from inside-out membrane patch excised from baso-lateral surface of a mouse submandibular acinar cell (reproduced from Maruyama et al 1983). The membrane potentials at which the current traces were obtained are given (in mV) to the left. The left column of current traces were recorded with $[Ca^{2+}] = 10^{-8}$ M in the solution in contact with the inner membrane surface, whereas the traces shown in the right column were obtained from the same patch after $[Ca^{2+}]$ had been elevated to 10^{-7} M. The picture shows Yoshio Maruyama together with Ole Petersen at a meeting in Okazaki, Japan in 1993.

suggested that this first direct demonstration of a voltage- and Ca^{2+}-activated K^+ channel in a transporting epithelium was of major functional significance, since Ca^{2+}-activation of the channel would enhance the opportunity for recirculation of K^+ taken up by the Na^+, K^+, Cl^- co-transporter and the Na^+,K^+ pump, whereas the voltage-sensitivity would provide a negative feed-back loop. Together this would allow very fine and acute regulation of transport thereby, for example, explaining the control of fluid secretion from exocrine glands. This theme was dealt with in much more detail in our subsequent review article for *Nature* (Petersen & Maruyama 1984), which became our most cited paper (ISI Citation Classic 1993), but this topic received its perhaps most definitive treatment in the annual review article I wrote for *The Journal of Physiology* (Petersen, 1992).

Looking back at my diary for 1983, I am amazed at the large number of invitations to deliver lectures in the US and throughout Europe that followed so quickly after the publication of the April 1983 *Nature* paper. In the summer of 1983, the IUPS Congress took place in Sydney and I, and very many other UK physiologists, made our way to Australia. This was many years before I became involved in running IUPS. At that time Schmidt Nielsen from the US was President and Scherrer from France Secretary General of IUPS. Otto Hutter was the UK representative on the IUPS Council. At that time I had, of course, no idea that I would eventually become very closely involved in the IUPS organization. The start of this was undoubtedly my period as Foreign Secretary of The Physiological Society (1992–1998). At the 1997 IUPS Congress in St Petersburg, I attended my first IUPS General Assembly as representative of the UK and my assistant, Nina Burdakova, organized and manned The Physiological Society stand at the Congress (Fig. 3). It is never possible to sum up briefly the multitude of events at an international congress. Every individual attending, depending on his or her research interests, will inevitably have a different experience. It is nevertheless clear, when inspecting the 1983 IUPS programme, that the then relatively new patch clamp technique was much in evidence at the congress. Erwin Neher gave one of the invited main lectures and in the many different symposia there were a substantial number of lectures on single channel current recordings from nerve, muscle and gland cells.

Calcium signalling, on the other hand, did not feature much at the 1983 Sydney Congress. To be sure there were several talks on voltage-gated Ca^{2+} channels, but at this point in time there were still not many reports on intracellular Ca^{2+} measurements and imaging of the intracellular $[Ca^{2+}]$ distribution was not technically possible. Nevertheless, 1983 became the effective starting point for the field that we now call Ca^{2+} signalling. This

Figure 3. The Physiological Society's stand at the IUPS Congress in St Petersburg in 1997. Sitting: Joan Abbott (left) and Nina Burdakova. Standing: Ole Petersen (middle) with two Bulgarian scientists supported at that time by The Physiological Society's Centre of Excellence Scheme.

development came late in the year with the publication of a paper in *Nature* jointly from the groups of Irene Schulz at the Max Planck Institute for Biophysics in Frankfurt and Michael Berridge and Robin Irvine at Cambridge University (Streb *et al* .1983). The paper showed that the small water soluble molecule inositol 1,4,5-trisphosphate (IP_3), can release Ca^{2+} from a non-mitochondrial store in permeabilized pancreatic acinar cells. The general significance of this observation was very quickly confirmed in many cell types by many different groups and led to a dramatic increase in the interest in Ca^{2+} signalling, which in subsequent years became, and still continues to be, a large and immensely productive research field. An important vehicle for publishing Ca^{2+} signalling work had in fact been created a couple of years earlier by Maynard Case. The journal *Cell Calcium* was established already in 1980 and it is a major credit to Maynard that he already at that time so clearly saw the potential for such a journal, which later benefited enormously from the discovery of the Ca^{2+}-releasing IP_3 effect as well as the invention of a new generation of fluorescent Ca^{2+} sensors that finally allowed high resolution Ca^{2+} imaging experiments to be conducted (Petersen *et al*. 2005). In 1993 the

Figure 4. The last night of the 2003 Gordon Research Conference on *Ca^{2+} signaling* in South Hadley, Massachusetts. From left to right: Katsuhiko Mikoshiba, Michael Berridge, Irene Schulz and Ole Petersen.

first Gordon Conference on Ca^{2+} signalling was held in New Hampshire and 10 years later, on the final night of the 2003 Ca^{2+} signalling Gordon Conference in Massachusetts, we celebrated the 20th anniversary of the discovery of the Ca^{2+} releasing action of IP_3 (Fig. 4).

2008

Now, 25 years after the start of The Physiological Society's magazine, the 'physiological world' looks in many ways very different from 1983. In the UK there are few free-standing physiology departments and in the 2008 RAE there is no specific physiology unit of assessment, but physiology is assessed by a 'Pre-clinical and Human Biological Sciences Panel' together with many other research fields. However, these developments should not necessarily be taken as an indication that physiology as a discipline is not doing well. As the President of IUPS and I have pointed out in a recent editorial for the journal *Physiology* (Kaneko & Petersen, 2007), the physiological journals are actually doing extremely well. As European Executive Editor of *Physiological Reviews* (*Physiol Rev*) I am certainly pleased that *Physiol Rev* is in the top 10 of ALL scientific journals with regard to Impact Factor (IF), ahead of – for example – all *Nature* review journals, except *Nature Reviews Cancer*. As described in the recent *Physiology* editorial, many other physiological journals have also seen healthy rises, some very substantial, in their IFs in recent years. Because physiology is THE integrative science and we have entered a period where the techniques exist for evaluating even very sophisticated integrative actions, for example in the brain of awake behaving animals (Ferezou *et al*. 2007), there is not the slightest doubt that the future of physiological research is very bright.

Figure 5. The IUPS Council at the Kyoto International Conference Center in December 2007, inspecting the venue for the 2009 IUPS Congress. From left to right, front row: Marjan Rupnik, Cecilia Hidalgo, Irene Schulz, Ole Petersen, Malcolm Gordon and Tai Yao; 2nd row: Aki Kaneko, Quentin Pittman, Sue Orsoni, Ann Sefton, Tony Macknight, Daniel Riquier and Antonio Campos de Carvalho.

2008 is not an international physiological congress year, but the preparations for the forthcoming 2009 IUPS Congress in Kyoto are almost finished (Fig. 5). One of the more imaginative symposia scheduled for the 2009 Congress which, I believe, contains many of the most crucial future elements of physiology, is entitled *Mapping of signalling networks* and is chaired by

Arthur Konnerth from Munich's Technical University and Hideo Mogami from Hamamatsu University in Japan. This symposium deals with the dynamic mapping of both large scale networks in the visual and barrel cortex (Ferezou *et al*. 2007) of the brain in awake behaving animals, as well as intracellular dynamic signalling networks (for example Ca^{2+} movements through various intracellular organelles (Park *et al* . 2008), protein kinase C and calmodulin translocation and substrate phosphorylation). Alexei Tepikin from Liverpool University, who has recently devised a clever fluorescent technique for monitoring dynamic Ca^{2+} concentration changes in single endocytic vacuoles in intact living cells (Sherwood *et al*. 2007) is one of the invited speakers in this symposium.

In 2008, we still have a Physiology Department in Liverpool, now headed by Susan Wray, but whereas there were only two professors in the Department in 1983 there are now nine professors! Personally, I am in the lucky situation of continuing to benefit from the MRC Professorship, which has freed me from all university administration and undergraduate teaching. This does not mean that 2008 will necessarily be an easier year than 1983, since work on the pre-clinical RAE panel, as well as several Royal Society committees and many other society involvements will take up a lot of time. Nevertheless, in 2008 – like in 1983 – I shall be speaking at a number of international symposia and congresses throughout the world. In addition to the considerable excitement of hearing about new scientific discoveries and integrating them into the physiological world picture, there will also be great pleasure in meeting up with many old and new friends from all over the world. One meeting I am particularly looking forward to this year is the symposium on *Frontiers in physiology* to be held at the Royal Danish Academy of Sciences and Letters in Copenhagen, the first academy that elected me as a member, 20 years ago. I am grateful to the American and the Scandinavian Physiological Societies for kindly sponsoring this symposium to celebrate my 65th birthday. The symposium will range widely, reflecting my interests, starting with molecular and cellular physiology, moving on to neurobiology, then on to cellular endocrinology and ending up with epithelial function. I am very happy that such an important figure as Bernd Nilius, who is leading the increasingly exciting TRP channel field, has agreed to give the Opening Lecture and that many other world leaders have accepted the invitation to speak. It will be a privilege to be together with an outstanding group of colleagues and friends from whom one can learn so much and the work being done, particularly by some of the younger invited speakers (Burdakov *et al*. 2006; CCH Petersen, 2007), gives me confidence that the future of physiology is in excellent hands.

Ole H Petersen
Department of Physiology, School of Biomedical Sciences, University of Liverpool, UK and President, The Physiological Society

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Determining control of the cardiovascular system in health and disease: from brain to blood vessel

Physiological Society Themed Meeting at the University of Leeds (17–19 March 2008)


Local hosts Susan and Jim Deuchars.

We extend a warm invitation to what we believe will be an exciting inaugural Physiological Society Themed Meeting here at the University of Leeds. We have lived and worked in Leeds for nearly 10 years now – we have loved every minute of it and hope that some of the great atmosphere in both University and city infuse the meeting.

The meeting

This is the first of the new style Physiological Society Themed Meetings which enables us to invite an internationally renowned cast to speak over a science-filled 2.5 day schedule. The meeting will take the form of five mini-symposia addressing the main theme, each lasting half a day. An important aspect is that each session has free communications drawn from submitted abstracts associated with it. These are traditional Physiological Society style talks lasting 10 minutes.

There are also poster sessions on each day. These communications are not necessarily restricted to the themes of the symposia and we will be happy to accept abstracts on any aspect of the cardiovascular, respiratory and autonomic control theme. During this meeting there will also be a lecture given by Andy Ramage in memory of David Jordan, an eminent and well respected Society Member who sadly passed away last year.

There will, of course, be plenty of opportunity to meet with colleagues informally. Leeds is not short of bars (from traditional Yorkshire to trendy modern) and restaurants to cater for almost any taste in food.

To further tempt you, the Sunday preceding the meeting (16 March) will see a Festschrift for Michael Spyer sponsored by The Society's journal, *Experimental Physiology*. For full information see p. 50.

The Institute of Membrane and Systems Biology (IMSB)

The meeting will be hosted by Sue and Jim Deuchars from the IMSB. The Institute is one of three research institutes in the Faculty of Biological Sciences at Leeds. It contains 46 academic staff (including independent research fellows) within two Research Groups – Integrative Membrane Biology and Cardiovascular and Sports Sciences. Interests are broad-ranging, from fundamental studies on the structures and functions of membrane proteins, to physiological questions in the mammalian cardiovascular and nervous systems – all the way to studies of health, exercise and disease in humans. To facilitate these studies there are also close links with physiologists throughout the University, located in the Faculty of Medicine and Health and elsewhere.

Further information

Society Meeting web site http://www.physoc.org/meetings/leeds2008
IMSB http://www.fbs.leeds.ac.uk/institutes/imsb
About Leeds http://www.leeds.gov.uk/About_Leeds.aspx
Brass band event http://www.leedsconcertseason.com
Leeds rugby http://www.leedsrugby.com

UNIVERSITY OF LEEDS

Invited speakers

Mike Andresen
Tom Cunnane
Susan Deuchars
Sheila Gardiner
Michael Gilbey
John Greenwood
Roger Hainsworth
Ida Llewellyn-Smith
Janice Marshall
Chris Matthias
Elspeth McLachlan
Shaun Morrison
Donal O'Leary
David Paterson
Julian Paton
Tony Pickering
Andy Ramage
Frederic Roche
Larry Schramm
Kevin Shoemaker

Symposia

Supraspinal control of autonomic outflow
Role of exercise in controlling autonomic function in health and disease
Spinal circuitry controlling sympathetic nervous activity
Effects of spinal cord injury on autonomic function
Autonomic function in the periphery

The Garstand Building (above) and Ilkley Moor (below).

The city

Leeds is often referred to as *the fastest growing city in the UK* and currently has a population of 750000 within the city boundaries. It has certainly changed in our time here and such change appears to be continuing apace. There is apparent commercial prosperity in areas of finance, business and media. This is all complemented by a vibrant mix of culture, commerce and style, making Leeds the primary social hub of the North. Leeds has just been voted as one of the top three places to shop in the UK by numerous independent surveys, and offers a huge range of shops and stores to suit all tastes. *The Lonely Planet* guide recently called it *the Knightsbridge of the North*.

If you are more inspired by country-side than shops, museums, clubs and pubs then not far away are the impressive Yorkshire Dales with awe-inspiring scenery and the huge selection of outdoor activities and pursuits.

Yorkshire is also home to the ancient city of York (about a 30 minute train ride away), with historical attractions such as the Viking and Roman heritage, the Minster, Shambles and a selection of Museums.

Yorkshire is famous for its brass bands and there is, in fact, a brass band performing in town during the meeting if you wish to sample it.

As with most British cities, sport is also a major pastime. The world famous Headingley stadium houses a premiership rugby union team (Leeds Carnegie), a premiership rugby league side (Leeds Rhinos) and top class cricket (Yorkshire Cricket Club). There is also a football team, Leeds United, at Elland Road. In fact, near the time of the meeting (14 and 20 March) there are two Leeds Rhinos matches – this could be a rare chance to take in some rugby league.

Jim Deuchars
Susan Deuchars
University of Leeds, UK

The Physiological Society Annual Meeting 2008

It is winter in Cambridge now, but the meeting organisers of The Physiological Society have been hard at work so that the main 2008 meeting here will be a splendid one for you!

Besides the exceptional Plenary talks, Prize Lectures and the Young Physiologists' Syposium, there will be many interesting and exciting Symposia to attend, including:

- New insights into nociceptors
- *NMDA receptors: building function from structure*
- pH dynamics in the central nervous system – a matter of life or death?
- *Regulation of placental function and pregnancy outcome*
- Cardiac cell effects of exercise training
- *The neural basis of reward and economic decision-making*
- Teaching Workshop – Systems physiology teaching and learning in the 21st century
- *On the perceptions of action and of affective touch, and their contribution to the somatic self*
- Novel concepts in potassium channel transport, targeting and recycling
- *Endothelial aging: molecular mechanisms and functional significance*
- Parental genetic influences on offspring growth, metabolism and energy homeostasis
- *Role of the t-tubules in subcellular modulation of cardiac excitation-contraction coupling*
- Recent advances in taste processing and recognition
- *Co-transmission in the autonomic nervous sytem*
- Information processing in the cerebellar cortical 'neuronal machine'
- *Hypothalamic regulation of mammalian fertility*

- Fuel for thought: current controversies in brain glucose sensing
- *Mouse models for human epithelial disease: novel insights and new horizons*
- Physical inactivity: a biological basis for metabolic disease.

More information about the meeting, the extensive social programme of extracurricular activities, and the host department will be published in the next *Physiology News* (PN 71).

But before then, don't forget the important dates given below.

See you in Cambridge this summer!

Bill Harris
Department of Physiology, Development and Neuroscience, Cambridge University, UK

Full information on Physiology 2008 is available at:
http://www.physiology2008.org

Abstract submission opens	**1 March 2008**
Abstract submission closes	**31 March 2008**
Travel Grants deadline	**31 May 2008**
Early registration closes	**6 June 2008**

Adventures in neurobiology with David Wallis

David Wallis (right) retired from the established Chair in Physiology at Cardiff University in 2000 where, for 33 years, his research was focused on neural signalling in mammals. His time at Cardiff saw the now-familiar evolution of an independent Department of Physiology into a facet of a larger School of Biosciences. Although these changes could provide rich material for the subject of a book, David has spent the last couple of years writing about the early part of his career as a PhD student studying animal behaviour and subsequent post-doctoral work on the electrophysiology of olfaction. Now that the manuscript is finished, he is embarking on the next step of finding a publisher for the book, which has the arresting title *In pursuit of the blood-red slavemaker – adventures in neurobiology*. After first learning that the blood-red slavemaker is a species of ant, Sarah Hall talked to David about his early research, pre-digital technology and the process of writing a scientific autobiography.

SH (**Sarah Hall**) What made you decide to spend your retirement writing your memoirs of your life in science?
DW (**David Wallis**) Good question! When I first retired, I wrote a local history of my home town of Stevenage and really enjoyed the writing experience, although it made me realise that if I was going to write any sort of scientific autobiography I needed to do it now, while there was still an opportunity to talk to the characters involved. Also, the whole process of conceiving, researching and writing the book has kept me – I would like to think – mentally alert and on the lookout for developments in the subject areas covered by the book.

Figure 1. A threat gesture – mandibles held wide open – shown by the ant on the left to an alien *fusca* from another colony. David Wallis faced threatening gestures from US Customs and Immigration officials when he arrived in New York to start his post-doctoral career.

SH Could you describe your book?
DW It recounts my early career during some crucial years in neurobiology. The book follows my career trail as it progressed from studies of ant behaviour to electrophysiological investigation of smell and taste in the blowfly. I hope I have provided an insight into the kinds of investigations that underlie the advance of science and a glimpse of the kinds of recording devices that were used at the time. It's really a collection of personal stories and anecdotes which illustrate the process of scientific research or, if you like, a history of science relating to a particular time and one person's experience.

SH Do you think it was a particularly exciting time?
DW It was – and that's part of the reason I tried to write the book. In the late 1950s there was a unique focusing together of psychologists, zoologists, neuroanatomists and, of course, physiologists, to try to understand neural processing. Ethologists in Cambridge, where I was studying, were excitedly debating new approaches and recent discoveries. From this foundation, I have retained a fascination with the mysteries of the nervous system throughout my career. I hope the book gives the reader an idea of what it is like to be part of a community of scientists engaged in an exploding area of knowledge. I hope it also illustrates how science proceeds not so much by amazing breakthroughs and flashes of inspiration, as through accumulation and integration of scraps of knowledge into a growing whole.

SH Has it been fun to revisit your early years in science?
DW Oh, yes! It has been a great opportunity for reminiscing. Some of the early technologies had aesthetic pleasures that have been lost in the digital era. I remember the thrill of achieving a perfect smoked drum record or capturing an oscilloscope trace on camera and developing the film successfully in the dark room. On the other hand, I also remember the trials associated with ageing the radio valves for the cathode followers in our recording apparatus, in order to minimise the noise interference.

My journey across the Atlantic on the *SS Bremen* to my post-doc position in Philadelphia was also unforgettable. The *Bremen* docked in New York and discharged her passengers into long queues at Customs and Immigration. Having eventually reached the front of the queue, I had my papers scrutinised and stamped, then I was allowed to continue on. As I left, I was mortified to realise that I was short of one stamp, so I went back to the queue I had just left and, thinking surely I don't have to line up again, I went to the front of the line to find the same official I had just seen. Uproar! Horror! Undesirable alien at large! Police shouted and converged on me waving their Tommy guns. A brief vision I had of being pumped full of lead was mercifully curtailed by the official recognising me ... welcome to the Land of the Free!

In those early years I met and learned from so many of the founding fathers in the fields of ethology and insect physiology, but at one time I also shared an office with a male bullfinch - it was being raised in the absence of birdsong as part of a study of song learning by my colleagues in the lab next door, so it grew up listening to me instead!

SH The book covers your early career and your post-doc activities in the USA, but your later career in physiology is not included. Is that the subject of the next book?
DW Maybe! That was a point in my career where there was a distinct end to a chapter. The considerations of my young family and the expiry of my visitor's visa in America meant that I returned to the UK, to work in Aberdeen with Hans Kosterliz, who was subsequently to lead his group towards the discovery of enkephalins. I was using my electrophysiological expertise, but now I was working in mammalian systems for the first time. This job also brought me into a physiology department for the first time, and I have remained a physiologist ever since.

SH The book is illustrated with some exquisite pen and ink drawings. Are you the artist?

Figure 2. Amazon ants (*Polyergus rufescens*, light colour) raiding a colony of *Formica fusca* (dark colour), whose nest is in dry soil under a stone. David Wallis's career in science began by studying such ant behaviour.

DW Yes, I have always enjoyed painting and drawing, and creating effective illustrations for the book has been part of the challenge of the whole project.

SH Who do you think will read this book?
DW The target audience is quite hard to define, and this is certainly something that potential publishers are struggling with. I suppose it's a popular science book for the educated reader, but it is nevertheless a scholarly text aiming to contribute to the history of the subject. I've tried to write in a style that is accessible to the general reader, and to explain any vital technical terms. The intention is to provide a personal approach that brings some of the innovators in neurobiology to life.

SH Has your experience of writing and publishing research articles helped?
DW Yes, but the publication side is very different. I have been advised to use an agent to submit the manuscript, rather than sending it off to the publishers myself. So far, I haven't been able to find an agent and have decided that it's not a promising avenue. I'm hoping to have a publisher soon, though. Any helpful advice would be welcome, as would any agent.

SH What next?
DW Well, I think there's a fascinating story to be told about the biology of serotonin, its discovery, its roles in the body and the evolutionary history of its receptors. I have mentioned the prospect of the '5-HT story' to a number of publishers but have yet to catch a fish with this particular worm. You never know, though ... watch this space!

David can be contacted at david.wallis@homecall.co.uk

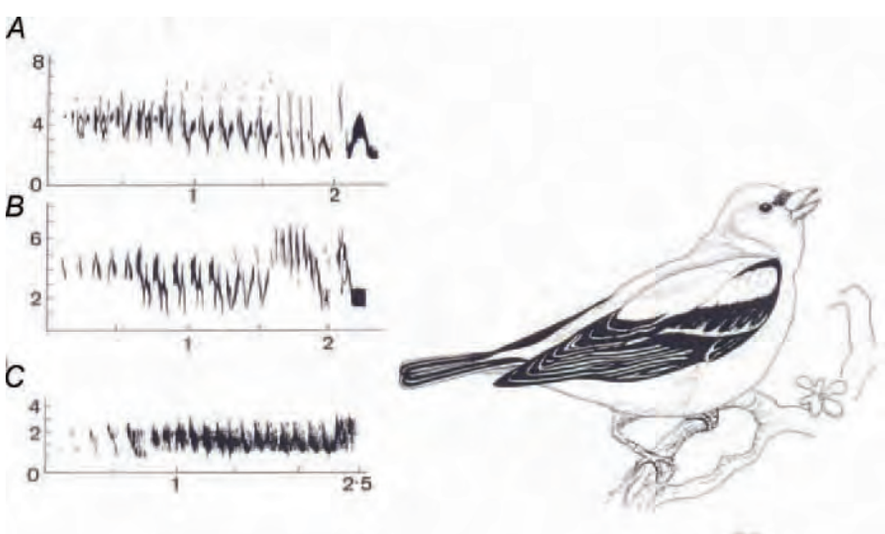

Figure 3. Sonograms of chaffinch songs showing learnt elaboration superimposed on the basic innate pattern. *A*, *B*, Normal full songs from wild caught birds. *C*, Song-pattern of bird hand-reared in visual and aural isolation from other birds (from Thorpe, 1956). David Wallis shared his office with a songbird.

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Five years in the life of a web site

IT Manager Liam McKay (right) looks back at the development of The Society's new site on the eve of its launch

2004

My first week at The Physiological Society was an interesting one. Having had a couple of days working in the Cambridge and London offices, I was invited to meet the then Chairman, Giovanni Mann. Newly in post himself, I sat in his office and the agenda was set with four words: new web site please.

Our existing web site, created in the mid 90s, had served its purpose for a number of years. The platform and programming on which the site resided gave The Society a means to present static textual information. Later came some dynamic content, such as the publication of our abstracts and the online version of the magazine you are now reading, which all proved popular.

However, as the years passed by, new web technologies meant new expectations of web sites. Web site users were slowly becoming accustomed to more professionally designed sites with improved navigation and accessibility. Organisations were keener to utilise an ever growing list of new features and functionality, such as secure online ordering, integration with back office systems and the delivery of a variety of multimedia content. A web site developed in the mid 90s was crying out for development by the mid 2000s!

2005–2006

Having spent my first year familiarising myself with the IT systems and needs of The Society, I felt confident to embark upon redeveloping our web site. It soon became apparent that the sky was the limit in terms of the number of features a new web site could have within a reasonable budget. We needed to focus on the aims of our site redevelopment. After meeting with staff and Executive Committee and Council members, we came up our aims.

External aims

- To give our web site a professional and user friendly design and navigation structure;
- To offer web site visitors secure online payment, membership subscription and renewal, and events booking;
- To offer our Members a community environment in which to communicate and share information.

Internal aims

- To fully integrate our back office databases with our front end web site;
- To allow non technical staff to input their own content;
- To develop a variety of online features that allow us to directly communicate Society business with our Members and site visitors.

Armed with these aims, I set to work obtaining proposals from a number of third party developers, most of whom I had encountered on visits to IT seminar and exhibitions. I also felt it important to forge relationships with fellow societies – what systems, features and providers were working well for them, and what were not.

Some of the proposals were expensive, some fell short, some were overly ambitious. One of the proposals came from our existing database supplier, Fisher Technology. By retaining our existing database and supplier relationship, both of which we were happy with, and utilising the web development services Fisher offered, their proposal won on both the functionality they could offer and the overall and ongoing costs of project.

2006–2007

The following year began with the development of a project plan. We initially had to indentify which features our site could benefit from. Fisher had a raft of choice: from forums to photo libraries, from bulletins board to news boards, from blogs to wiggets – they could even provide bliggets (yes, you've guessed it – a bligett is a widget with

Figure 1. Something old: the existing Society web site.

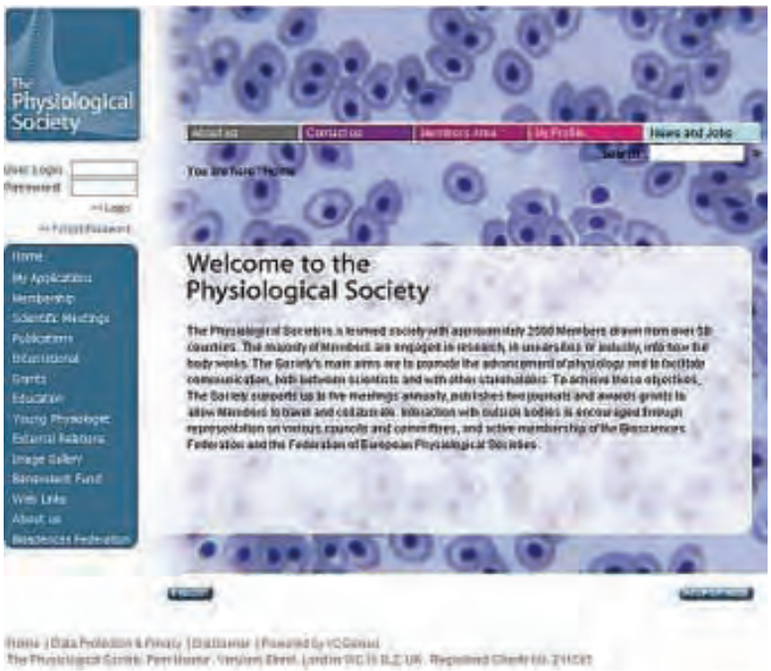

Figure 2. Something new: the redeveloped Society web site.

a blog). A lot of choice, a lot of avenues to pursue.

Based upon our web statistics we knew which areas of our current site got regularly high usage. Areas such as the news and jobs listings, the online magazine, our meetings programme and international section all prove popular.

We also wanted to develop an online community feel for our Members. Features such as forums, blogs, bulletin boards, profile pages, and a searchable Member directory would give Members a portal through which to communicate and share information.

Another key aim was integrating our office procedures and Member database into our new web site. Many of our current processes, such as membership and grants applications, events registration, and membership renewals, involve a lot of office administration. By transferring these manual procedures to an automated system, Members would be able to input their information directly online, which in turn would activate a completely online review process ending in direct input into our database. Such technology would dramatically reduce administrative time, increase the accuracy of the information we hold, whilst giving our Members a speedy, secure and efficient online experience.

We were also keen to give our staff the ability to create and edit online content without the need for programming or design skills. Staff were emailing me copy or creating content in applications such as Microsoft Word, only for me to duplicate this online. By allowing staff to input content directly into templates using a simple online content management application, duplication of work is removed.

After many review meetings with Fisher and staff, a detailed picture of all our procedures was created. From our initial aims, a final proposal was created and fine-tuned. Each element of the site was included into a project plan with associated costs, time and people resources required.

The next stop was to deliver the proposal to our Executive Committee and then to Council. The plan was positively received. A need had clearly been identified and final approval to proceed with the project was given. Now the real work began!

Over the next 18 months, elements of the site were developed. Working with 35 Communications, the agency involved in our recent rebranding, we were able to create the new look for our site. Features were slowly added to a test site, then tested, fine tuned, retested, fine tuned again, and retested. Nothing could be signed off until it was unbreakable!

Of course, with a project of this size, problems were encountered. Some elements of the site, in particular, online membership application took much longer to get right than anticipated. However, slowly, but surely, we made careful progress.

2008 and beyond

2008 was the year light could be seen at the end of the tunnel. Many elements of the site had been completed, and final testing of our membership application and events registration processes were underway.

We have recently moved to an online system for tracking progress on the final elements of the site that need correcting – a thankfully short list. The site has really taken the shape of what we originally envisaged, and something very different from its current incarnation!

We are now looking forward to a launch. We decided, through experience, not to promote a 'go live' date until now. I am pleased to announce the last week of March 2008 as our new site launch. We will be contacting all our Members with information on the array of features nearer this date.

We have already been thinking about future developments to the site: online movie streaming, podcasts, an educational resource portal, integrated wikis and facebook – the list grows. However, for the time being, I am confident our new web site will give our Members the online experience they can expect from a modern society site.

Liam McKay
IT Manager, The Physiological Society

Cold facts about AMPK in fat

Adenosine monophosphate activated protein kinase (AMPK) has been called the 'metabolic master switch', and 'cellular fuel gauge' because of its ability to sense intracellular energetic stress in the form of a decreased ATP/AMP ratio and respond by increasing ATP synthesis and decreasing ATP consumption (Hardie & Carling, 1997). Here recent findings that AMPK is highly abundant in brown adipose tissue and regulated in novel ways in both brown and white adipose tissue are discussed. These findings suggest possible novel roles for AMPK in regulation of body weight, body temperature, and pathogenesis during hyper-adrenergic states.

AMPK activity in brown adipose tissue

During the last 15 years, studies conducted largely in liver and muscle have shown that activation of AMPK stimulates ATP producing reactions such as free fatty acid oxidation, while inhibiting ATP consuming processes. This has led to the perspective that high AMPK activity is associated with a state of cellular energy conservation. Brown adipose tissue is in some ways the antithesis of an energy conserving tissue since its uncoupled metabolism converts reducing equivalents into heat instead of useful chemical energy (ATP), in a process termed non-shivering thermogenesis. Thus it was surprising to find that α1 AMPK expression and activity in BAT is the highest yet for any reported tissue, being 3-fold higher than in liver (Mulligan *et al*. 2007). This AMPK activity is entirely attributable to the α1 isoform, occurs in multiple species (Fig. 1) and appears to be secondary to high levels of expression of the protein.

While currently we can only speculate as to the physiological role this high level of AMPK activity plays in brown adipose tissue, it is accompanied by extremely high levels of its downstream target,

Kurt Saupe (far right) with his lab group.

acetyl-coA carboxylase (ACC), the rate-limiting step in fatty acid synthesis (ACC1) and inhibition of fatty acid oxidation (ACC2). Both ACC isoforms are heavily phosphorylated (inhibited) in brown adipose tissue, presumably by AMPK. Such a massive pool of ACC would be ideal for the simultaneous lipogenesis and β-oxidation that takes place on a large-scale during non-shivering thermogenesis. Upon induction of non-shivering thermogenesis, selective dephosphorylation of ACC1 by an unknown effector might rapidly release the inhibition of fatty acid synthesis, while ACC2 remains inhibited by AMPK, allowing β-oxidation. It is also tempting to speculate that a high AMPK activity is necessary to maintain the high mitochondrial density present in brown adipocytes. This speculation is based on reports that AMPK activates PGC-1α, a transcription factor central to mitochondrial biogenesis (Jager *et al*. 2007).

AMPK activity in brown adipose tissue during acute and chronic cold exposure

A main function of brown adipose tissue is generation of heat via non-shivering thermogenesis during times of environmental cold exposure. During acute cold exposure this response includes a large increase in oxidation of free fatty acids. Given the established role of AMPK in regulating free fatty acid oxidation in tissues such as liver and muscle, one might anticipate that activation of AMPK would be needed to allow the increase in free fatty acid oxidation during the first hours of cold exposure. Instead, during the first 1–24 hours of exposure to 4° C, AMPK activity does not increase, suggesting that further activation of AMPK above the high basal level is not necessary for the initial induction of non-shivering thermogenesis. It should be noted that in cultured brown adipocytes adrenergic stimulation increases the amount of phosphorylated AMPK within minutes (Hutchinson *et al*. 2005). However, the meaning of this intriguing finding is unclear since *in*

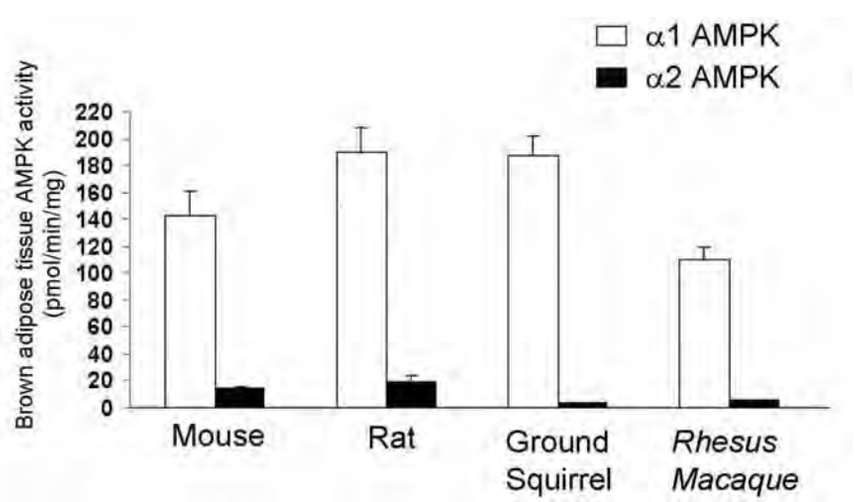

Figure 1. Comparable levels of AMPK activity in brown adipose tissue across mammalian species. Enzymatic activity of the two isoforms of AMPK measured in brown adipose tissue of four species of mammals (n=5-8). In all four species, the α1 isoform had a very high level of activity in absolute terms, and when compared to the activity of the α2 isoform.

vivo no increase in AMPK activity occurs during the first hours of cold exposure.

Chronic cold exposure causes brown adipose tissue to remodel in a way that increases its heat generating capacity including tissue hypertrophy, mitochondrial biogenesis and upregulation of UCP1 and other enzymes important for non-shivering thermogenesis. We found that the expression and activity of AMPK increases significantly in brown adipose tissue in response to chronic (7–14 day) cold exposure. Critical insight into the physiological role of AMPK in brown adipose tissue will likely come from determining which of the many cell types within brown adipose tissue contain high levels of AMPK activity that are further upregulated in response to chronic cold exposure. While one might assume that it is the brown adipocytes, this has not yet been established.

Chronic cold-induced upregulation of AMPK also raises the questions of whether the high AMPK activity observed in brown adipose tissue at 'baseline' is in part a response to the relative cool temperature at which experimental mice are usually housed (approximately 5° C below their thermoneutral temperature), and whether chronic environmental heat exposure might cause down-regulation of AMPK in brown adipose tissue.

What is the mechanism by which chronic cold exposure increases AMPK activity in brown adipose tissue? Since most, if not all, cold-induced changes in brown adipose tissue biology are mediated by a cold-induced increase in sympathetic nerve activity, we tested whether the effects of cold on AMPK activity could be reproduced by sympathomimetics. However, neither chronic norepinephrine nor the β3-adrenergic agonist CL 316,243 administered to mice for 14 days using implanted micro-osmotic pumps caused an upregulation of brown adipose tissue AMPK activity. This despite the fact that these

	Cold	Norepinephrine	CL 316,243
Liver	No		
Brown adipose tissue	Yes →	No	
White adipose tissue	Yes →	Yes ——→	Yes

Figure 2. Mechanisms upregulating tissue AMPK activity are highly tissue specific. Environmental cold exposure (14 days at 4°C) significantly increases α1 AMPK activity in both white and brown adipose tissue but not liver. This upregulation can be mimicked pharmacologically in white adipose tissue (epididymal fat pad) by chronic administration of either norepinephrine, or the β3-adrenergic specific agonist CL 316,243.

sympathomimetic drugs caused the expected upregulation of UCP1 levels. This indicates that upregulation of AMPK does not go hand-in-hand with upregulation of UCP1 and other enzymes linked to non-shivering thermogenesis, and suggests the existence of an alternative non-sympathetic mediated pathway for cold-induced gene regulation in brown adipose tissue.

Link between sympathetic nervous system and AMPK in WAT

While white adipose tissue was once regarded largely as an inert storage depot for excess energy, it is now recognized as an organ central to the etiology of diseases such as type 2 diabetes mellitus. A major part of this new understanding comes from the recognition that white adipose tissue is an endocrine organ that depending upon its state of 'health', produces variable amounts of the adipokines that regulate factors such as appetite and insulin sensitivity. We found that in white adipose tissue AMPK activity was robustly upregulated by chronic cold exposure, as it was in brown adipose tissue (Fig. 2). However, in contrast to brown adipose tissue, administration of norepinephrine for 14 days *in vivo* significantly increased white adipose tissue AMPK activity. To our knowledge, this is the first demonstration of an *in vivo* link between these two important stress response systems. To identify the adrenergic receptor subtype responsible for this effect, the β3-specific agonist CL 316,243 was administered. It too was sufficient to increase AMPK activity in white adipose tissue, narrowing the search for the relevant cell type to those containing β3-adrenergic receptors (white and brown adipocytes). However, it seems unlikely that the brown adipocytes located within white fat increase AMPK in response to β3 adrenergic stimulation since β3-adrenergic stimulation does not upregulate AMPK in brown adipose tissue.

Significance for human pathophysiology

AMPK is now recognized to play a key role in regulating aspects of whole body energy balance such as appetite (Minokoshi *et al*. 2004). A role for AMPK in regulating caloric expenditure by brown adipose tissue may be a second way in which AMPK contributes to the regulation of body weight. Given the central role of AMPK in regulating cellular metabolism, its high activity in brown adipose tissue suggests the intriguing possibility that by manipulating AMPK activity one could regulate the number of calories dissipated as heat. 'Firing up' brown adipose tissue to treating obesity in humans has gained support from a recent report identifying small, distinct regions of brown adipose tissue in humans – primarily in the area of the collar bone and along the spine (Nedergaard *et al*. 2007). Future studies will be required to determine what role AMPK in brown adipose tissue plays in regulating body weight and body temperature.

Congestive heart failure, metabolic syndrome and obesity are often hyperadrenergic states that cause desensitization of adrenergic signaling in peripheral tissues. Our data raise the intriguing possibility that desensitization of adrenergic

signaling might lead to a loss of AMPK activity in the white adipose tissue of these patients. The idea that loss of AMPK activity can be central to pathology is supported by the successful clinical use of the AMPK activators metformin and thiazolidinediones to treat type 2 diabetes (Musi & Goodyear, 2006). Currently, we are at the very early stage in understanding how AMPK activity is regulated in adipose tissues, and the (patho)physiological meanings of this regulation. As during the last decade, our perspective on AMPK continues to expand, with a new focus on its multiple roles in whole body energy balance.

Kurt W Saupe
Jacob D Mulligan
Departments of Medicine and Physiology, University of Wisconsin, Madison, WI, USA

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Mulligan JD, Gonzalez AA, Stewart AM, Carey HV & Saupe KW (2007). Upregulation of AMPK during cold exposure occurs via distinct mechanisms in brown and white adipose tissue of the mouse. *J Physiol* **580,** 677–684.

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Insight into how the human retina obtains its need of vitamin B1

The retina has a substantial need for a variety of nutrients, including vitamin B1. This vitamin is involved in a variety of metabolic reactions and, thus, is essential for normal functions and well-being of the retina. Hamid Said (below) and colleagues examined how human retinal epithelial cells transport the vitamin, how the transport process is regulated, and what happens when clinical mutations in a thiamin transporter (that occur in the genetic disorder thiamine-responsive megaloblastic anemia) affect the ability of this membrane protein to function as a transporter of the vitamin

The human retina is a highly differentiated (specialized) tissue whose cells are considered to be among the most metabolically active in the human body. Due to the central role it plays in vision, the retina is protected from the fluctuations in the surrounding environment by what is called the blood-retina barrier (BRB). This barrier also controls access of nutrients, growth factors and hormones to the different cells of the retina. Retinal pigment epithelia (RPE) represent an important part of the BRB and separate the outer retina from its choroidal blood circulation. This single layer of epithelial cells plays many physiological functions that include transport of nutrient/substrates into and from the retina. In order to perform such an important function, cells of the RPE have developed a host of specialized systems for transporting nutrients/ ions/ substrates across their plasma membranes. A defect in the ability of these systems will have negative consequences on the well-being of the retinal tissue (Meire *et al*. 2000; Scharfe *et al*. 2000). Thus studies into how these systems function, how they are regulated and what intracellular and extracellular factors that affect/regulate their function are of significant importance. Knowledge in these areas has been forthcoming in recent years, especially following the establishment of appropriate cell lines for use in *in vitro* investigations. Such preparations have eliminated the problems associated with the limited supply of appropriate human RPE cells, their limited survival in culture, the low homogeneity of the primary preparations of these cells, and the tendency of such primary cells to lose their epithelial phenotype with time in culture.

Our recent study examined the mechanism by which vitamin B1 (thiamine) is taken up by cells of the human RPE, determined the molecular identity of the membrane transport systems involved in the process, and identified intracellular and extracellular factors that affect (regulate) the vitamin uptake process (Subramanian *et al*. 2007). Thiamin is an important micronutrient for the well-being and health of the retina. As with all other cells of the human body, retinal cells cannot synthesize thiamin and thus must obtain the vitamin from the surrounding environment. The vitamin plays an important role as a cofactor in a variety of intracellular metabolic reactions including those involved in energy metabolism. The vitamin also has the ability to reduce cellular oxidative stress and to prevent apoptosis (programmed cell death). Thus, reduction in the level of thiamin in retina cells leads to

disturbance in cellular metabolism. Such a reduction in intracellular thiamin level occurs in the genetic disorder of thiamine-responsive megaloblastic anemia (TRMA; also known as Roger's Syndrome), and leads to retinal abnormalities and visual disturbances in the affected subjects. The cause of TRMA is due to mutations in the human thiamin transporter-1 (hTHTR-1) (Diaz *et al*. 1999; Fleming *et al*. 1999; Labay *et al*. 1999), a major player in moving thiamin into a variety of cell types.

Results of the Subramanian *et al* studies showed for the first time the existence of an efficient and specific transport process for the internalization of thiamin into cultured human-derived retinal pigment epithelial cells (hRPE). This process was found to be mediated via the function of the two transport systems, the hTHTR-1 and the human thiamin transporter- 2 (hTHTR- 2). These studies also showed that the thiamin uptake by the hRPE cells is adaptively up regulated (turned on) when the cells are maintained in conditions of low thiamin availability via a mechanism that involves activation of genes of both the hTHTR- 1 and hTHTR- 2 (i.e., the *SLC19A2* and *SLC19A3* genes, respectively). To understand how clinical mutations in the hTHTR-1 that are found in TRMA affect the function of this thiamin transporter and how the cells process the mutant proteins, these investigators generated these mutants experimentally (by means of site-directed mutagenesis) then introduced (transfected) them into cultured hRPE cells. They then followed the movement of the fluorescently labeled proteins inside the living cells by mean of imaging using confocal microscopy. The results showed that these mutations lead to malfunctioning of the hTHTR-1 (Fig. 1*A*). This was found to be due to either the inability of the cells to move the mutated proteins to the cell membrane or that the cells do move the mutated proteins to the cell membrane, but that the proteins not functional (Fig.1*B*). Collectively, results of these studies lay the foundation for further investigations into ways to improve the delivery of the vitamin to cells of the human retina, especially in disease conditions associated with low cellular thiamin homeostasis.

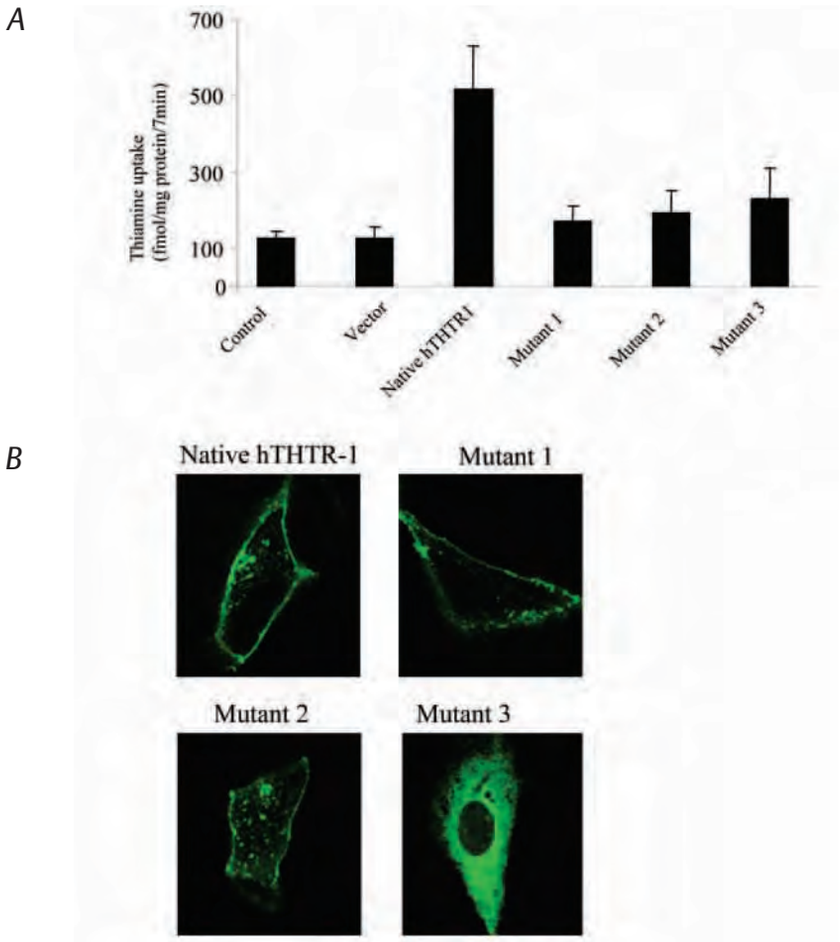

Figure 1. Distribution of individual clinically relevant hTHTR-1-GFP mutants (fused to the green fluorescent protein, GFP) in the human retinal pigment epithelial ARPE-19 cells. *A*, uptake of ^{3}H-thiamine in control ARPE-19 cells and those transiently expressing vector (GFP), native hTHTR-1 (hTHTR-1-GFP), mutant 1 (hTHTR-1[D93H]-GFP), mutant 2 (hTHTR-1[S143F]-GFP), mutant 3 (hTHTR-1[G172D]-GFP). *B*, representative confocal lateral (*xy*) images showing localization of individual mutant constructs in ARPE-19 cells, 24-48hrs after transient transfection.

Hamid M Said
Departments of Medicine and Physiology, University of California School of Medicine, Irvine, CA, USA

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Selectivity: a sticky affair?

In analogy to some ionic channels, substrate selectivity in ion-coupled cotransporters appears to imply a low flux rate. However, in the presence of potassium the hornworm KAAT1 transporter reconciles selectivity and high transport rates, writes Antonio Peres (below)

The problem of coupling high selectivity with high flux rate in ionic channels has been clarified by Roderick MacKinnon, who received the Nobel prize in 2003 for his studies on the potassium channel KcsA (MacKinnon, 2003). Fig. 1*A* illustrates the structure of the selectivity filter of KcsA, formed by the 'potassium signature' residues TTVGYG. Each of the four subunits that constitute the oligomeric assembly contributes four main-chain carbonyl atoms that surrogate the interactions between K^+ ions and water in the bulk solution. The resulting organisation of the K^+ binding sites in the pore, in addition to providing selectivity by way of its intrinsic electrostatic properties, also allows high throughput, because the proximity of the potassium sites causes the ions to hop from one

place to the next due to charge repulsion.

This elegant demonstration confirms an explanation proposed many years before, on the basis of purely functional observations: that of *selectivity by affinity* (Hess & Tsien, 1984). This idea developed from results on Ca^{2+}-selective channels: how was it possible for a channel to choose Ca^{2+} over Na^+, an ion with similar dimensions but much more concentrated in the extracellular medium? The observation that when Ca^{2+} was absent Na^+ ions were able to generate a much larger current through the same channels led to the notion of a 'sticky' channel, i.e. to the idea that the pore contained a high-affinity binding site for Ca^{2+}.

This was later identified in a ring of four glutamates (the EEEE motif), each located in the same relative position of the P-loops of the four homologous domains of the protein. Structural modelling of this region (Lipkind & Fozzard, 2001) showed that a Ca^{2+} ion is strongly bound by the carboxyl oxygens of the glutamates (Fig. 1*B*). At physiological Ca^{2+} concentrations, however, this electrostatic trap is weakened by the simultaneous presence of two other Ca^{2+} ions bound to two flanking low-affinity sites, allowing a significant flux to occur.

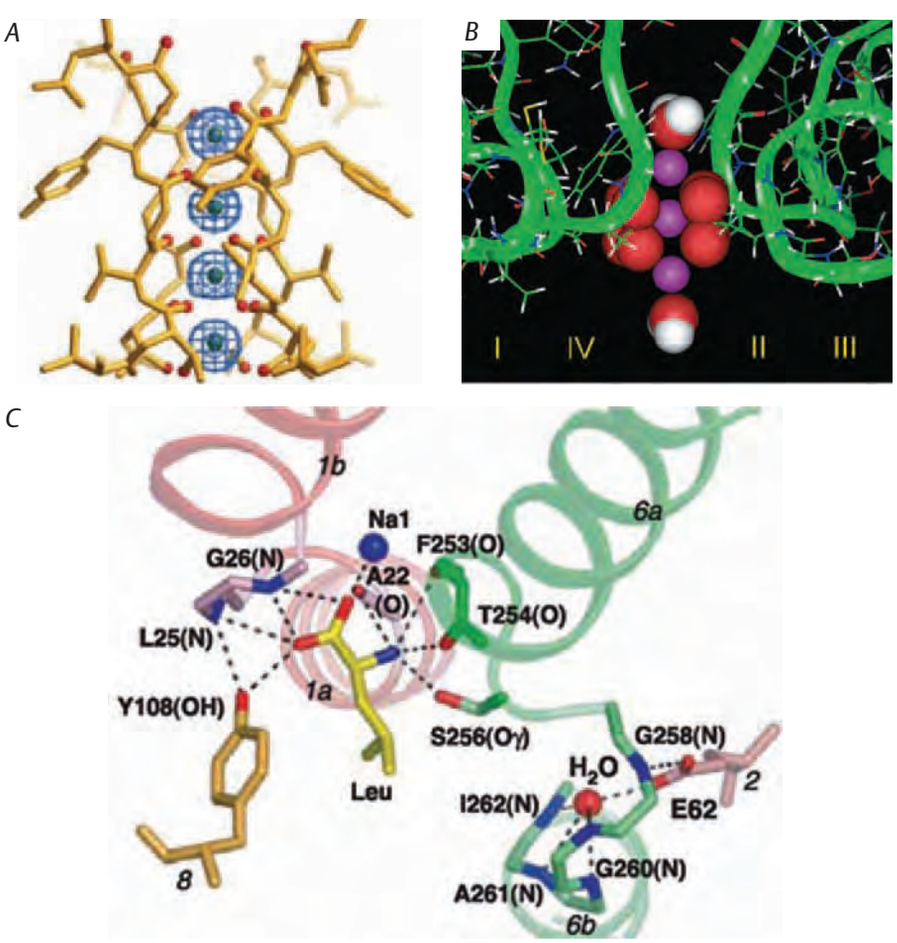

Figure 1. *A*, atomic structure of the selectivity filter of the KcsA channel; the four blue meshes show the allowed position of dehydrated potassium ions (only two positions are normally occupied) (reprinted from Mackinnon, 2003. Copyright 2003, with permission from Elsevier). *B*, homology modelling in the L-type calcium channel suggests that the Ca^{2+} ion bound to the EEEE motif (central violet ball surrounded by eight red balls representing the carboxyl oxygens) is flanked by two other Ca^{2+} ions bound to lower affinity sites (upper and lower violet balls). In this arrangement the electrostatic trap formed by the oxygens is weakened and ion flux may occur (reprinted, with permission, from Lipkind & Fozzard, 2001. Copyright 2005 American Chemical Society). *C*, structure of the binding site of the $LeuT_{Aa}$ transporter showing the participation of a sodium ion (Na1) in the interaction with leucine (reprinted by permission from Macmillan Publishers Ltd: *Nature* [Yamashita *et al*. 2005], copyright 2005).

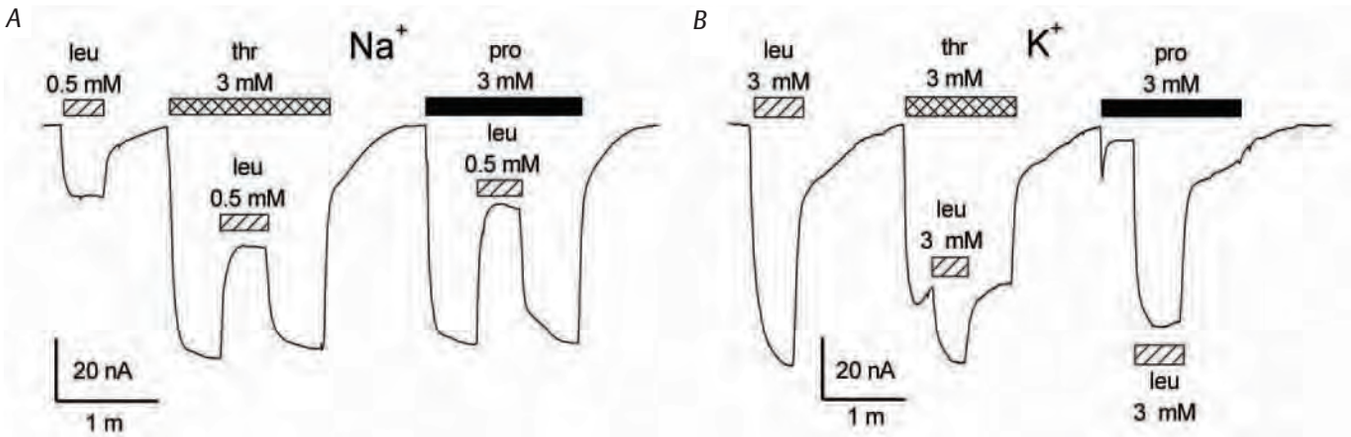

Figure 2. Recordings of inward transport currents elicited by leucine, alone or in combination with threonine or proline, in an oocyte expressing KAAT1, when the driver ion is Na^+ (*A*) or K^+ (*B*). In Na^+ solution the presence of leucine together with proline or threonine reduces the current amplitude approximately to the level of leucine alone, while in K^+ solution, leucine causes currents that approach the higher leucine-alone level. All substrate concentrations are saturating. (Adapted from Miszner *et al*. 2007).

Thus, K^+ channels and Ca^{2+} channels appear to teach us that efficient discrimination among similar ion species requires a toll in terms of a significant reduction in conductivity, and that further structural specialisations are needed to increase flux rate.

Selectivity in transporters

The application of electrophysiological and biophysical approaches to the study of electrogenic cotransporters is a relatively young area of research, that has become possible following the cloning of the proteins of interest and their overexpression in heterologous systems. This delayed start has offered in return the advantage of finding ready-to-use ideas and rationales that had been previously developed in the field of ionic channels. Many analogies between channels and transporters have been found, such as channel-like behaviour of transporters, transient currents reminiscent of the gating currents of voltage-dependent channels, and properties compatible with single-file permeation mechanisms.

The observations described in our recent paper (Miszner *et al.* 2007) point to a further possible analogy between transporters and channels, namely that selectivity by affinity may constitute a useful idea also in understanding the functioning of transporters.

Indeed, the competition experiments reported by Miszner *et al*. strongly recall the Ca^{2+} block of the current carried by other ion species in the Ca^{2+} channel (Hess & Tsien, 1984). The neutral amino acid transporter KAAT1, cloned from the midgut of the larva of the invertebrate *Manduca sexta*, has a rather wide spectrum of transportable substrates and, in addition, is able to exploit either the Na^+ or the K^+ electrochemical gradients as energy sources for active transport. In this transporter leucine acts as a dominant substrate: although in presence of Na^+ threonine and proline may be transported at higher rates, the concomitant presence of leucine, even at a lower concentration, reduces the amplitude of the transport-associated current to the level produced by leucine alone (Fig. 2*A*).

This electrophysiological observation is confirmed by radioactive uptake experiments, that show that in presence of both leucine and threonine, or leucine and proline, only leucine is actually translocated. Quite interestingly, the negative dominance seen in presence of Na^+, is reversed in presence of K^+: in this condition the leucine-associated current is higher, and addition of leucine increases the amplitude of the currents elicited by threonine or proline alone (Fig. 2*B*). This last finding represents a variant with respect to the paradigm relating high selectivity and low flux rate, and will require better knowledge of the substrate-transporter interactions and of the conformational changes involved in the substrate translocation.

KAAT1 belongs to the SLC6A family of transporters, a bacterial member of which, $LeuT_{Aa}$, has been recently crystallized and its atomic structure resolved (Yamashita *et al.* 2005). On the basis of the leucine binding site of $LeuT_{Aa}$, and examining the differences in sequence between KAAT1 and CAATCH1 (a very similar transporter in which leucine act as a blocker), we have identified serine 308 in KAAT1 (S256 in $LeuT_{Aa}$ and T308 in CAATCH1) as a critical residue for leucine transport. Replacing S308 in KAAT1 with the threonine present in CAATCH1 converts leucine from a transported substrate to a blocker. Indeed in a transport system whose selectivity is based on high-affinity binding sites, the difference between a permeating species and a blocker may be rather subtle, as shown by Ca^{2+} ions in Ca^{2+} channels (Hess & Tsien, 1984). The S308T mutation in KAAT1 may simply increase the strength of leucine binding to such an extent that translocation or dissociation very rarely occur, thereby blocking the transporter.

The amino acid corresponding to KAAT1 S308 has been found to play

an important role in substrate selectivity in other transporters of the family as well. The two glycine transporters GlyT1b and GlyT2a may be distinguished by their differential ability, shown by the former but not by the latter, to transport also sarcosine. Replacing serine 481 of GlyT2a (corresponding to S308 of KAAT1) with the glycine present in GlyT1b makes GlyT2a capable of sarcosine transport, while the reverse mutation G305S in GlyT1b suppresses sarcosine transport (Vandenberg *et al.* 2007). Furthermore, the creatine transporter CRT may be induced to transport GABA by a number of selected amino acid substitutions, among which the replacement of glycine 318 (corresponding to S308 of KAAT1) with the alanine present in the same position in the GABA transporter GAT1 (Dodd & Christie, 2007).

It appears, therefore, that position 256 of $LeuT_{Aa}$, located in the unwound region of the sixth transmembrane segment, plays a fundamental – though not exclusive – role in determining substrate specificity in a number of SLC6A transporters.

In ionic channels selectivity and permeation involve only two chemical species, the ion and the protein. Conversely, in cotransporters at least three actors are involved: the protein, the ion(s) and the organic substrate. This is very clearly demonstrated in the snapshot of the structure of $LeuT_{Aa}$ (Fig. 1C), in which a Na^+ ion is shown to participate in shaping the leucine binding pocket. Furthermore, the controversial role of Cl^- ions in this family of transporters is beginning to be elucidated as an optional fourth component, in those transporters of this family that lack an acidic residue in the position corresponding to E290 of $LeuT_{Aa}$ (Forrest *et al.* 2007; Zomot *et al.* 2007).

Indeed, as already noted (Kilic & Rudnick, 2000), whereas ions present a symmetrical surface to the pore walls of the channel, the small organic molecules that are translocated by cotransporters are generally highly asymmetric and would consequently require an asymmetrical binding site. It is not a surprise then that while the pore of the K^+ and Ca^{2+} channels is at the centre of a tetrameric assembly, each subunit of the oligomeric transporters appears to function independently (Yamashita *et al.* 2005; Boudker *et al.* 2007). The lack of symmetry in transporters implies greater complexities in the number and types of interactions among the distinct molecular entities involved. The recent definition of the atomic structure of $LeuT_{Aa}$ has offered the tools for the study of these interactions, and the challenge is now to understand their dynamics during the transport cycle.

Acknowledgement
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Antonio Peres
Department of Biotechnology and Molecular Sciences, University of Insubria, Varese, Italy

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Managing without 'water receptors'

At an unrecorded meeting in the late 1940s or early 1950s Yngve Zotterman reported the discovery of water receptors in the tongue of the frog.

Jack Eccles in the audience commented that, as someone from a very thirsty country, he was very pleased to hear about these receptors. 'Panzee' Wright, later Professor of Physiology at Melbourne University (who was ever a generous and convivial host) immediately objected that he had never heard of an Australian drinking water.

In later years Zotterman discovered that, although these water receptors were present in several species, they were absent in humans and rats. No doubt Jack and Panzee nevertheless continued to enjoy slaking their thirst, each in his own way.

Liam Burke
Sydney, Australia

Breaking the barrier; the role of actin filaments in somato/dendritic peptide release

In many cells actin filaments are organised in a dense web beneath the plasma membrane and can be transiently depolymerised in response to stimulation, suggesting that actin filaments provide a barrier for vesicles to access sites of release

The magnocellular neurons of the hypothalamic supraoptic and paraventricular nuclei secrete the neuropeptides vasopressin and oxytocin from the posterior pituitary gland into the general circulation. The pioneering work of David Pow and John Morris (1989) indicated that these peptides are also released directly into the hypothalamus, and the major source of this central release are the dendrites of magnocellular neurons. Over the last decade, studies have amplified the data on dendritic peptide release and revealed many aspects of its control and function. It appears that part of the function of dendritically-released neuropeptides is to autoregulate the electrical activity of the cells of origin, as both neuropeptides act directly on their respective neurons via specific receptors and modify their excitability. In addition, neuropeptides persist in the brain extracellular fluid for relatively long periods and are able to diffuse considerable distances. In a hormone-like fashion the peptides may act on more distant brain regions concerned with behaviours that are known to be influenced by oxytocin and vasopressin. Most often these regions richly express peptide receptors, but they are innervated by few, if any, oxytocin or vasopressin containing projections.

Although it has been known for more than 20 years that there is local release of vasopressin and oxytocin within the hypothalamus, it is only in recent years that the molecular and cellular mechanisms that mediate dendritic release have begun to be understood. While electrical activity in the cell bodies is generally accompanied by release from axon terminals, release from dendrites is generally not. Dendrites appear to have release properties different from those of axon terminals, and release appears to be enhanced if calcium has been released from intracellular calcium stores, suggesting that the release mechanism can be 'primed'. Priming causes vesicle movement into pools from where they can be released more readily by subsequent stimuli for a prolonged period in large quantities (Ludwig & Leng, 2006).

When Pow and Morris showed that peptide release from magnocellular neurons was not restricted to any particular part of the plasma membrane, they noted that regulation of exocytosis may rely on controlling the access of the vesicles to the plasma membrane. This led to the suggestion that this control may be exerted by cytoskeletal elements, as in classical endocrine cells. In addition to a network throughout the cytoplasm, the cell bodies of magnocellular neurons possess a network of filamentous or F-actin beneath the plasma membrane. In endocrine cells, this cortical F-actin engulfs secretory vesicles, segregating them from the plasma

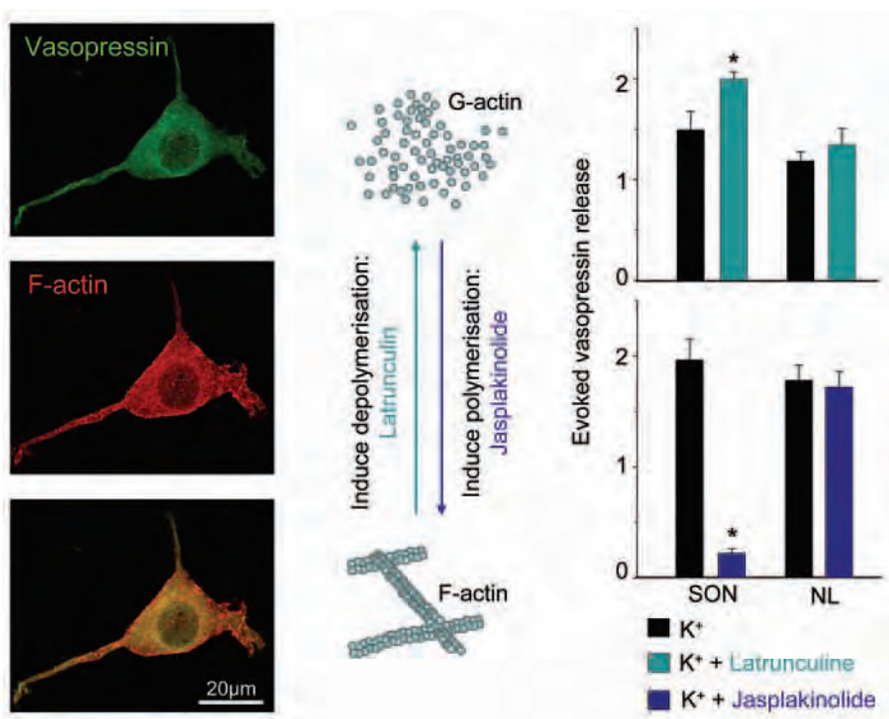

Figure 1. Immunohistochemical detection of vasopressin and F-actin (visualised by fluorescently tagged phalloidin) in an isolated magnocellular vasopressin cells. To investigate a role of F-actin depolymerisation in regulating evoked (high potassium) peptide release from magnocellular neurons *in vitro*, we used latrunculin B, a toxin from marine sponges that sequesters actin monomers. To determine the effect of F-actin polymerisation, jasplakinolide, a membrane permeable cyclic peptide that promotes the formation and/or stabilisation of F-actin filaments, was used. F-actin depolymerisation significantly enhanced high K^+-induced somato/dendritic vasopressin and oxytocin release (data for oxytocin are not shown) within the supraoptic nucleus (SON), whereas F-actin polymerisation inhibited peptide release. Vasopressin and oxytocin secretion from axon terminals of the neural lobe (NL) was not altered by any of the treatments, suggesting that high-K^+ evoked release in the SON, but not the NL, requires opening of the F-actin barrier.

membrane. As F-actin undergoes fast, transient and reversible depolymerisation during hormone secretion, and areas of exocytosis have been found to be lacking F-actin, cortical F-actin has long been proposed to act as a barrier, restricting movement of secretory vesicles to their release sites at the plasma membrane (Aunis & Bader, 1988; Vitale *et al*. 1995).

In magnocellular neurons, the cortical F-actin of the somata/dendrites is rapidly and reversibly depolymerised by factors known to stimulate secretion (e.g. depolarisation by high potassium). Moreover, depolymerisation of F-actin with latrunculin stimulated oxytocin and vasopressin secretion from both the axon terminal and dendritic compartment. Acute treatments with jasplakinolide inhibited stimulated dendritic peptide release; however, there was no effect on release from axon terminals. Thus the evoked release from somata/dendrites requires depolymerisation of F-actin (Tobin & Ludwig, 2007). Our data are consistent with other preparations, such as insulin secretion from β-cell lines and isolated rat islets.

However, there is evidence that the F-actin cortex, classically viewed as a barrier that hinders the movements of granules to the plasma membrane, might also play a positive role by providing either 'tracks' permitting docking at appropriate sites, or by spatially constraining components of the exocytotic machinery. This suggests that activation of secretion does not simply trigger the disassembly of the barrier, but rather a reorganisation of F-actin which allows the granules access to the exocytotic sites and provides the structural support necessary for exocytosis. In the magnocellular system, it appears that F-actin remodelling plays a part in regulating the availability of functionally mature and readily-releasable vesicles in different parts of the cell and thus is involved in the differential control of secretion from different parts of the cell. Given that release of vesicles from both the somata/dendrites and axon terminals in magnocellular neurons does not appear to occur at morphologically distinct active zones (as described for neuronal synapses), actin filaments could provide transport, tethering, barriers and support structures at different times and locations.

Once again the magnocellular neurons of the supraoptic nucleus have proved to be a tractable preparation for revealing important aspects of neuronal function. These were among the first cells to provide evidence that endocrine cells containing peptides could also act as neurons. Their terminals in the posterior pituitary provided a readily accessible preparation for pioneering studies on stimulus-secretion coupling.

Now, studies indicate that these cells are again leading the way in revealing that dendrites can take their place as full players in both the transmitting and receiving stages of cellular communication.

Mike Ludwig
Vicky Tobin
Centre for Integrative Physiology, University of Edinburgh, Edinburgh, UK

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IUPS 2013

Readers may remember that, at the IUPS San Diego meeting in 2005, we successfully bid to host the 2013 IUPS meeting. Since then we have been negotiating with conference sites and I am pleased to announce that the meeting will be held from 21–26 July at the International Convention Centre (ICC) in Birmingham (pictured below). Not only is the ICC an excellent conference centre, but it is in the recently refurbished Birmingham City Centre, surrounded by restaurants and pleasant canal side walks.

We want the 2013 meeting to be a celebration of physiology. Our original bid had the (only slightly tongue in cheek) subtitle of *Back to the future* . The development of powerful modern techniques in genetics, imaging, etc. allows us to address the questions that have interested physiologists for 150 years and IUPS 2013 will highlight this.

There is much to do. So far, planning has been in the hands of the IUPS 2013 Steering Committee consisting of David Eisner (Chair), Graham McGeown, Ian McGrath, Prem Kumar, Bridget Lumb, Clive Orchard and Ole Petersen, with day- to-day organization by The Society's Events Team – Nick Boross-Toby (Manager), David Bennett and Heidi Adnum. In the next year or so we will set up the various organizing committees, including a Programme Committee. At this time we would be grateful for input from readers. Are there things that you particularly like and/or hate about IUPS and other large meetings? Do you have suggestions for what we should do? Above all please take every available opportunity to let your colleagues know about the meeting. Please feel free to submit comments by email to dbennett@physoc.org.

See you in 2013!

David Eisner

Coupling or not coupling of mitochondria to Ca^{2+} sources in neurones. Soma and neurites differ

Bioluminescence imaging of aequorin targeted to mitochondria shows that these organelles are closely coupled to the endoplasmic reticulum in the soma but not in the neurites of sympathetic neurones. This functional organization could contribute to generate spatial differences in neuronal Ca^{2+} signals

Ca^{2+} signals play a pivotal role in neuronal functions including excitability, secretion, learning and memory. They are triggered by the opening of plasma membrane, voltage-operated Ca^{2+} channels (VOCCs) and amplified by Ca^{2+}-induced Ca^{2+} release (CICR) from the endoplasmic reticulum (ER). It is becoming evident that, in addition to their role as cell powerhouses and central players in the intrinsic pathway for apoptosis, mitochondria are essential for modulation of Ca^{2+} signals. However, research on mitochondrial Ca^{2+} homeostasis has been hampered by technical constraints and the difficulty for accurate monitoring of mitochondrial Ca^{2+}, particularly in single neurons. The introduction of protein Ca^{2+} probes targeted to mitochondria has paved the way for better understanding of mitochondrial Ca^{2+} signalling (Rizzuto *et al*. 1998).

Mitochondria can take up Ca^{2+} through the mitochondrial Ca^{2+} uniporter, a low-affinity, high capacity system that permits Ca^{2+} uptake towards the huge electrochemical gradient built at the inner mitochondrial membrane by the respiratory chain. As Ca^{2+} uptake by mitochondria requires relatively high cytosolic Ca^{2+}, it was believed for a long time that mitochondria did not play a role in Ca^{2+} signalling under physiological conditions, being only able to buffer large, pathological Ca^{2+} overloads. However, recent evidence has shown that mitochondrial Ca^{2+} influx follows almost always normal, 'physiological', cytosolic Ca^{2+} increases. To explain these findings it has been proposed that high Ca^{2+} microdomains are transiently

Lucía Núñez (above left) Carlos Villalobos (above) and Javier García-Sancho.

generated near mitochondria close enough to the mouth of the Ca^{2+} channels at sites of Ca^{2+} entry or release. The Ca^{2+} concentration at these hot spots would be high enough to activate rapid Ca^{2+} uptake through the uniporter in surrounding mitochondria. For example, mitochondria in close contact with ER take up Ca^{2+} from high Ca^{2+} microdomains in the mouth of the Ca^{2+} release channels opened by IP_3 (Rizzuto *et al*. 1998).

Aequorins with low affinity for Ca^{2+} were initially developed for monitoring high Ca^{2+} levels inside the ER, but their targeting to mitochondria revealed two important new concepts in mitochondrial Ca^{2+} homeostasis (Montero *et al*. 2000). First, that only a pool of mitochondria, the one close enough to sites of Ca^{2+} entry and release, is able to 'sense' the high Ca^{2+} microdomains. This mitochondrial pool takes up Ca^{2+} avidly, whereas the remaining mitochondria do not see the Ca^{2+} hot spots and take up much less Ca^{2+}. Second, that the increase in mitochondrial Ca^{2+} in the sensitive mitochondrial pool may reach as much as 10^{-3} M, a value 100 fold larger than previous estimates. In fact, a quantitative estimation of the Ca^{2+} redistribution after stimulation of chromaffin cells suggested that most of the Ca^{2+} entering cells through VOCCs is actually cleared from the cytosol by the surrounding mitochondria rather than by other extrusion systems (Villalobos *et al*. 2002). In chromaffin cells, the same mitochondrial pool is functionally coupled to VOCCs and ER. This organization may help to avoid spreading of entering Ca^{2+} towards the cell core and to tune up local ATP synthesis to power exocytosis.

Ca^{2+} signalling in neurones can be even more complex. It has been proposed that distinct intracellular Ca^{2+} transients in neurites and somata may integrate neuronal signals (Johenning *et al*. 2002). The mechanisms underlying the generation of spatially specific Ca^{2+} signals is not well understood. Mitochondria modulate cytosolic Ca^{2+} signalling in neurons by buffering the Ca^{2+} rises evoked by Ca^{2+} entry or Ca^{2+} release. This was indirectly suggested by the increase in the cytosolic Ca^{2+} responses after preventing mitochondrial Ca^{2+} uptake with protonophores in sensory neurons (Shishkin *et al*. 2002). The low level of bioluminescent light emission by aequorin has hampered imaging of mitochondrial Ca^{2+} in individual neurons for a long time. However, combining the use of ultra-sensitive photon counting cameras with high-efficient protein expression systems has enabled recently imaging of individual neurons expressing targeted aequorin (Núñez *et al*. 2007). Fig. 1 shows the photonic emissions imaged from sympathetic

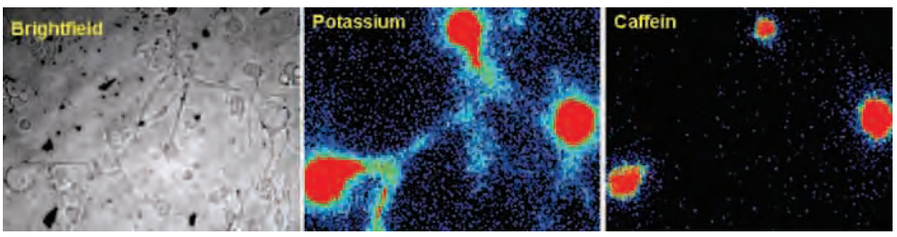

Figure 1. Imaging of photonic emissions reflecting mitochondrial Ca^{2+} increases in the soma and neurites of sympathetic neurons expressing mitochondria-targeted aequorin. Neurons from adult mouse superior cervical ganglion expressing aequorin targeted to mitochondria were stimulated with high K^+ solution or caffeine. High K^+ induced mitochondrial Ca^{2+} increases in the soma and the neurites whereas caffeine promoted mitochondrial Ca^{2+} increase on in the soma. The bright field image is shown at left (see Nuñez *et al*. 2007 for details).

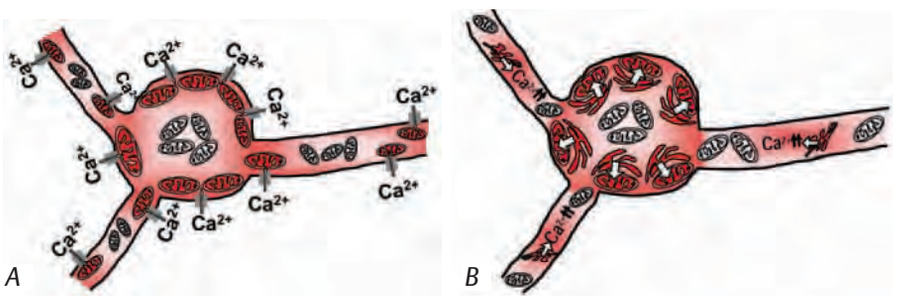

Figure 2. Coupling of mitochondria to ER and plasma membrane in the soma and in the neurites. In the soma, a pool of mitochondria is located close to the sites of Ca^{2+} entry and release. The other pool is distant and hardly senses the high Ca^{2+} domains. In neurites mitochondria are functionally coupled to plasma membrane Ca^{2+} channels but not to sites of Ca^{2+} release. Thus, Ca^{2+} release is buffered by mitochondria in the soma but not in neurites, leading to region-specific cytosolic Ca^{2+} increases. The colour intensity is meant to be proportional to Ca^{2+} concentration. Calcium filled organelles are the coloured ones. *A*, calcium entry through calcium channels; *B*, calcium release from intracellular stores.

neurons expressing aequorin targeted to mitochondria. The neurons were stimulated with either high-K^+ solution, which depolarises the plasma membrane and triggers Ca^{2+} entry trough VOCCs, or with caffeine, which stimulates Ca^{2+} release from the ER. Both stimuli triggered photonic emissions, which reflects the mitochondrial Ca^{2+} uptake induced by Ca^{2+} entry or Ca^{2+} release. Only a subpopulation (30–40%) of mitochondria 'sensed' these stimuli, suggesting the existence of two different pools of mitochondria, one functionally coupled and the other not coupled to the different Ca^{2+} sources.

Interestingly, mitochondria at soma and neurites behaved differently. Whereas mitochondria in the soma were stimulated by caffeine, mitochondria at neurites were not. These differences were not seen when the neurons were stimulated with high K^+ (Fig. 1). As a consequence of the lack of mitochondrial buffering, the cytosolic Ca^{2+} rise induced by caffeine was larger in the neurites than in the soma (Núñez *et al*. 2007). These results agree with previous reports where mitochondria seemed to buffer Ca^{2+} entry but not Ca^{2+} release in dorsal root ganglion neurons (Svichar *et al*. 1997). In summary, these results suggest that strategic location of mitochondria in different regions of the neuron may contribute to the generation of spatially specific Ca^{2+} signals (Fig. 2). For example, direct measurements in cell bodies and in the proximal and distal dendrites of cerebellar Purkinje neurons showed that amplification due to CICR is more efficient as the dendritic branches become thinner. Whether local mitochondria take up Ca^{2+} or not may have important physiological consequences. Apart from the buffering of the cytosolic Ca^{2+} signal, the increase in mitochondrial Ca^{2+} promotes local ATP synthesis that may be required for exocytosis. In addition, Ca^{2+} taken up by mitochondria is released later back to the cytosol. This delayed enhancement of cytosolic Ca^{2+} has been suggested to be involved in post-tetanic potentiation. Thus, coupling or not coupling of mitochondria to the different Ca^{2+} sources may lead to region-specific modifications of Ca^{2+} signals that may underlie important neuronal functions.

Lucía Núñez
Carlos Villalobos
Javier García-Sancho
Instituto de Biología y Genética Molecular, University of Valladolid and Spanish Research Council, Valladolid, Spain.

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Exercise-induced adaptations in tendon tissue

Training induces changes in the mechanical and biochemical characteristics of tendon tissue. What mechanisms are involved and are these changes in proportion to skeletal muscle hypertrophy?

Katja Heinemeier (left) and Jens Olesen

It is well known that regular exercise can lead to hypertrophy of skeletal muscle, and there is a relatively good understanding of the mechanisms involved in this adaptive process. But what happens with the tissues that support the skeletal muscle when strength is increased as a result of training? Tendons, which connect muscle to bone, are essential for transmission of force and storage of elastic energy during muscle contraction, and it seems logical that they should adapt along with the muscle tissue, to keep the muscle-tendon unit functioning.

It is clear that tendon tissue responds to loading, but while the adaptive response in muscle tissue relates closely to the loading stimulus, the tendon's response appears far less sensitive.

Long-term training does seem to induce changes in both the mechanical and biochemical characteristics of tendon tissue. Several studies indicate that the tendon becomes stiffer (so that it elongates less at a certain amount of applied force) (Magnusson *et al.* 2007), and in animals a greater maximal load can be sustained by the tendons (Wang, 2006). Changes in the mechanical tendon properties can be related both to an increase in cross sectional area and to changes in the tendon tissue 'quality'. In line with this, training-induced tendon hypertrophy has been shown in animals, and in humans the cross sectional area of Achilles tendons in individuals who regularly perform weight-bearing exercise is larger than in sedentary individuals (Magnusson *et al.* 2007). The loading-induced hypertrophy of the tendon tissue is presumably based on an increase in the local synthesis of type I collagen – the main 'building-block' of tendon tissue – as both acute exercise and long-term training appear to induce the production of this protein (Langberg *et al.* 1999; Langberg *et al.* 2001).

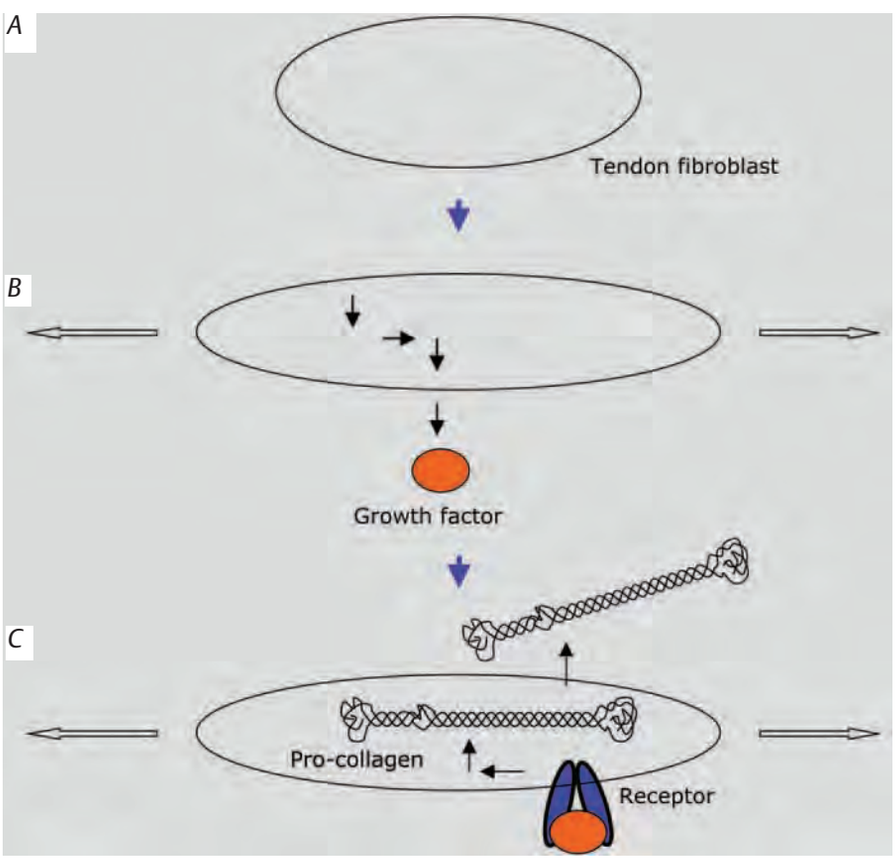

Figure1. Possible mechanism for loading induced collagen synthesis in tendon tissue. Based on the knowledge from *in vitro* studies, it is hypothesized that tendon cells embedded in the tendon extra cellular matrix, *A*, will be stretched during muscle contractions and respond to this stimulus by altered intracellular signalling, represented by black arrows, ultimately leading to increased expression of collagen-inducing growth factors (e.g. TGF-b-1), *B*. This will lead to stimulation of collagen production by the autocrine action of the newly synthesized collagen inducing growth factors , *C*.

Possible role of collagen inducing growth factors

One of many unanswered questions is how exercise/training can lead to increased production of collagen in the loaded tendon tissue.

In vitro studies indicate that certain collagen-inducing growth factors, including transforming growth factor-β-1 (TGF-β-1), connective tissue growth factor (CTGF), and insulin like growth factor-I (IGF-I), are candidates to act as mediators of mechanically induced collagen synthesis in connective tissue (Chiquet *et al.* 2003). These growth factors are produced by fibroblasts *in vitro* in response to mechanical stimuli, and they can subsequently induce the expression of collagen in the mechanically stimulated cells (by autocrine stimulation) (Fig. 1). This mediator role is especially well documented for TGF-β-1, and a recent study shows that mechanically induced collagen synthesis in cultured patella tendon fibroblasts is directly dependent on TGF-β-1 function (Yang *et al.* 2004).

In a recent study we aimed to investigate whether TGF-β-1, CTGF

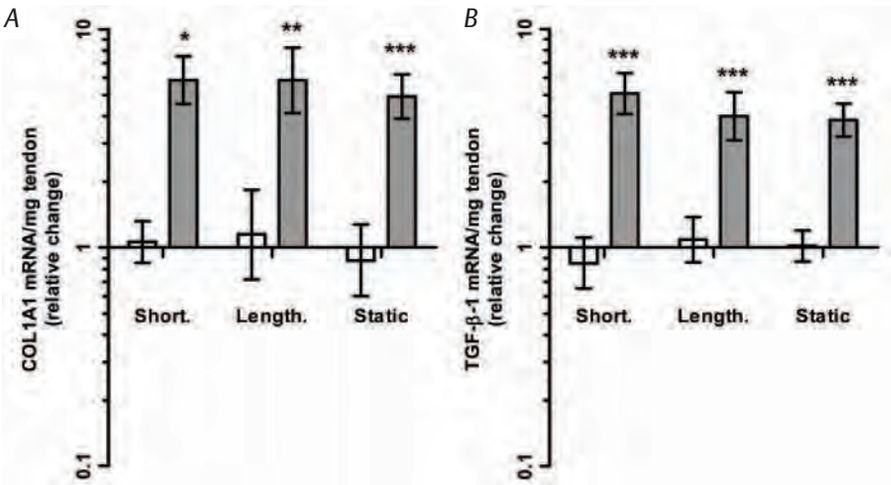

Figure 2. Expression of type I collagen and TGF-b-1 in rat Achilles tendon after strength training.
COL1A1 mRNA (*A*) and TGF-b-1 mRNA (*B*) normalised to tissue weight in rat Achilles tendons after a 4-day unilateral plantar-flexion resistance training program of either shortening, lengthening or static contractions (grey bars) vs. contra lateral controls (white bars). Values are geometric means ± SE, and data are presented as fold changes relative to the mean of all control values (*p<0.05, **p<0.01, ***p<0.001).

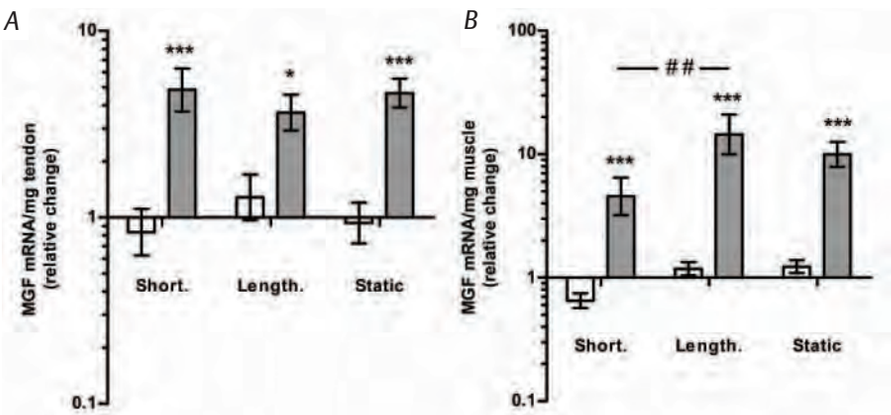

Figure 3. Expression of mechano growth factor (MGF) in rat Achilles tendon and gastrocnemius muscle after strength training
MGF mRNA normalised to tissue weight in rat Achilles tendon (*A*) and gastrocnemius muscle (*B*) after a 4-day unilateral plantar-flexion resistance training program of either shortening, lengthening or static contractions (grey bars) vs. contra lateral controls (white bars). Values are geometric means ± SE, and data are presented as fold changes relative to the mean of all control values (*p<0.05, ##p<0.01, ***p<0.001).

and the IGF-I isoforms – IGF-IEa and mechano growth factor (MGF) – could be involved in the loading-induced changes in collagen production in tendon tissue *in vivo*. We found that the level of mRNA for type I collagen was substantially increased in rat Achilles tendons after a 4-day plantar-flexor strength training programme (Fig. 2). At the same time the expression of TGF-β-1 and IGF-I isoforms (IGF-IEa and MGF) were increased, while no change was found in the level of CTGF mRNA (Fig. 2 & 3). These results underline that loading of tendon structures can induce the expression of collagen and suggest a potential role for TGF-β-1 and the IGF-I isoforms in mediating this effect (Heinemeier *et al.* 2007a; Heinemeier *et al.* 2007b).

Tendon 'quality' and collagen cross-linking

Changes in tendon mechanical properties do not necessarily depend on changes in tendon size. Several studies have shown a markedly increased tendon stiffness without any increase in tendon cross sectional area (e.g. Reeves *et al.* 2003), and although these results are still debated, it is likely that repeated loading can lead to changes in the properties of the tendon tissue matrix. In line with this, it has been suggested that an increase in the number of cross-links between collagen molecules could be part of the tendon response to mechanical loading. This would lead to stabilization and strengthening of the fibrillar collagen structures and thus to increased stiffness of the tendon matrix.

Lysyl oxidase is essential for the formation of cross-links between newly formed collagen molecules, and we have found that the expression of this enzyme is induced more than 35 fold in rat Achilles tendons in response to 4 days of resistance training (Heinemeier *et al.* 2007a). This finding definitely supports that an increase in cross-link formation could be an important part of the adaptive process in loaded tendons. In fact, it may be speculated that collagen turnover is increased in response to loading (Langberg *et al.* 2001) to give the opportunity to assemble new collagen fibres with a higher content of cross-links. Such a response could explain a training-induced increase in stiffness without changes in cross sectional area.

Can tendons keep up with muscle?

There is no doubt that tendons respond to repeated loading. But how well does the tendon response correspond with the response of the skeletal muscle tissue?

In the rat training study discussed above, three different types of muscle contractions – shortening, lengthening and static contractions – were applied. With this setup the lengthening contractions led to a substantially greater force production than the shortening contractions, while the static loading led to an intermediate force production. We found that the expression of growth regulatory factors, IGF-IEa, MGF and myostatin, in the trained muscle tissue was highly reflective of the force production (Fig. 3). Surprisingly

however, in tendon the expression of both collagen, growth factors, and lysyl oxidase was equally induced with all training types and thus unrelated to force production (Figs. 2 & 3) (Heinemeier *et al.* 2007a;Heinemeier *et al.* 2007b). In other words it appears that tendons, compared to muscles, are relatively insensitive to the degree of mechanical stimulus, and it could be speculated that the tendon adaptation will not 'keep up' with the muscle adaptation if muscle contractions with high loads are performed repeatedly. This may help explain the high incidence of tendon overload injuries in sports.

In summary, repeated loading appears to change the mechanical characteristics of tendons. These changes could be explained by an increased tendon cross sectional area – possibly relating to a growth factor-induced collagen production – but also by changes in the tendon tissue matrix, such as increased levels of cross-linking between collagen molecules. Importantly, the tendon tissue seems less sensitive than skeletal muscle to changes in mechanical stimulus.

Katja M Heinemeier[1]
Jens L Olesen[2]
[1]Institute of Sports Medicine, Bispebjerg Hospital, Copenhagen, Denmark and [2]Department of Rheumatology, Aalborg Hospital, Aalborg, Denmark

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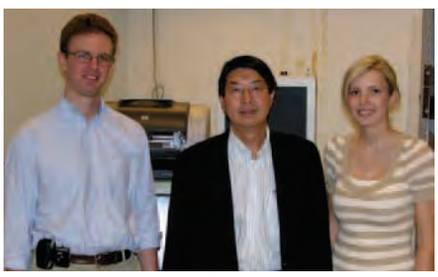
Modifying the excitability of motor cortex with direct current stimulation

In recent years there has been an increase in interest in techniques that can modify the excitability of the motor cortex. It is widely believed, with some experimental evidence, that if the excitability of the cortex can be increased then rehabilitation strategies after neurological insults may be more efficacious. Three techniques have emerged, or re-emerged, that offer the potential to modify the excitability of the cortex: repetitive transcranial magnetic stimulation (rTMS), paired associative stimulation (PAS) and direct current stimulation (tDCS). While the first two of these approaches may act through spike-timing dependent plasticity (at least for PAS), the third approach is different in nature. In this strategy, a comparatively low level constant DC field is applied across the motor cortex through electrodes placed on the scalp. The time course of the intervention and the effects are similar across all three protocols, with each intervention lasting about 10 minutes and its effects lasting for around an hour. Clinically tDCS shows considerable promise since the effects appear comparable to other cortical excitability modifying protocols but the equipment is substantially cheaper than that required for either PAS or rTMS. Since the intervention does not require the application of any large magnetic fields, it can be applied to a wider population, including those who have had neurosurgical aneurysm clipping (i.e. in some stroke and traumatic brain injured patients).



Jonathan Norton (left), Ming Chan and Hollie Power.

We have recently shown that DC stimulation affects the cortical control of a movement, as assessed by intermuscular coherence (Power *et al.* 2006). Typically the currents applied at the scalp are of the order of 1mA. The two electrodes are positioned over motor cortex, contralateral to the muscle/limb of interest and over the opposite forehead (i.e. ipsilateral to the muscle/limb of interest). In Fig. 1 we illustrate a tDCS experimental set-up, and typical results from an experiment in which cathodal stimulation was applied. Briefly, there is a decrease in the amplitude of the MEPs, area of β-band coherence and region of activation of the cortex assessed using fMRI. In this review, we will examine some of the recent evidence regarding the possible cellular mechanisms of action of tDCS (Fig. 2).

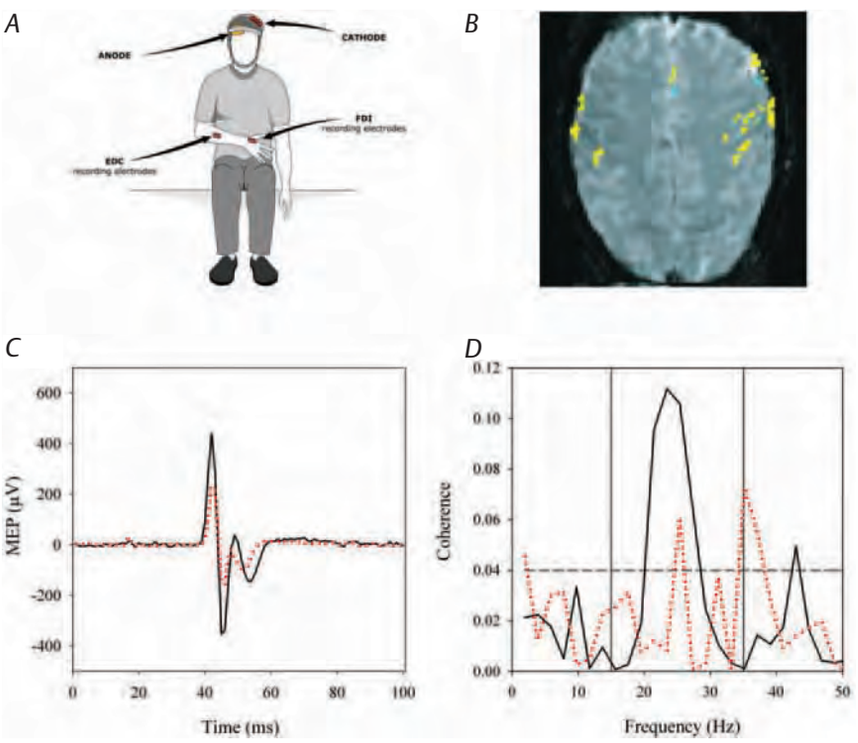


Figure 1. Experimental setup of tDCS and typical results from cathodal stimulation. *A*, depicts the setup for tDCS stimulation on the scalp and recording electrodes in the contralateral arm. *B*, shows the results of fMRI (Baudewig *et al.* 2001). During a figure tapping task following cathodal stimulation, the area of activation in the motor cortex became substantially suppressed (blue pixels) compared to baseline (yellow pixels). Correspondingly, the size of the motor evoked potential (MEP) from transcranial magnetic stimulation in panel C (subject at rest) and β-band intermuscular coherence obtained during weak static contraction of the EDC and FDI muscles shown in panel D were reduced following cathodal tDCS (red dotted line) compared to baseline (black solid line).

It appears that the response to tDCS is not just at the level of the pyrimdal tract neuron (PTN) itself but rather primarily at the level of the interneurons projecting onto the PTNs, since tDCS does not alter the amplitude of TES-evoked MEPs. NMDA-glutamate receptors are known to be important for the induction of cortical neuroplasticity in long-term potentiation and depression. Strikingly, administration of the NMDA receptor-antagonist dextromethorphane completely eliminated both the short- and long-lasting after-effects of tDCS, independent of stimulation polarity (Liebetanz *et al.* 2002; Nitsche *et al.* 2003). In addition, GABAergic mechanisms are also likely involved in the after-effects of tDCS as Nitsche *et al.* (2004) showed that administration of lorazepam, a $GABA_A$ receptor

agonist, resulted in late enhancement of excitability following anodal tDCS. The reasons for the delay are not clear, even though remote mechanisms such as connections with cortico-thalamic and nigrostriatal neurons could be at play because they primarily use GABA as their inhibitory neurotransmitter. In contrast, cathodal tDCS after-effects were not affected by lorazepam. Since benzodiazepines do not directly activate GABA receptors themselves, but rather facilitate the transmission of already active receptors, this finding cannot exclude inhibition of the GABAergic system in the cathodal after-effects.

Several animal studies have demonstrated the importance of dopaminergic mechanisms in NMDA receptor-mediated neuroplasticity. Similarly, studies examining various types of learning have shown that dopaminergic systems are important in human neuroplasticity. Nitsche *et al.* (2006) found that by administering a D2-receptor antagonist, sulpiride, the after-effects of tDCS were completely abolished. However, co-administration of pergolide, a D2/D1-receptor agonist with sulpiride, could not re-establish the excitability changes induced by tDCS, indicating that D1 receptor activation alone is not capable of restoring tDCS after-effects. In contrast, when pergolide was administered alone without sulpiride, it caused the tDCS-generated excitability changes to last for up to 24 hours after stimulation, suggesting that activation of D2-receptors has a consolidation-enhancing effect on the excitability changes induced by tDCS. These findings are potentially interesting because the administration of D2 agonists may allow use of tDCS as a therapeutic tool to produce sustained changes in motor cortical excitability.

Additionally, non-synaptic mechanisms are likely also involved in the after effects of tDCS. Liebetanz *et al.* (2002) showed that

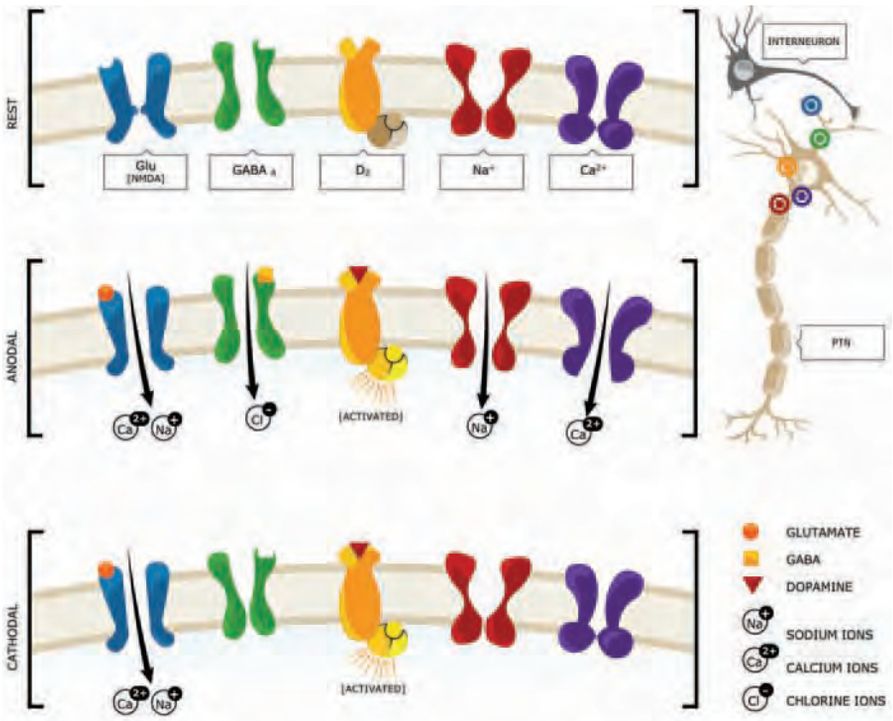


Figure 2. Mechanisms of tDCS. Locations of the relevant receptors and ion channels on the pyramidal tract neuron (PTN) are shown in the top right drawing. While the NMDA, $GABA_A$ and dopamine 2 receptors, sodium and calcium channels all play a role in response to anodal stimulation, only NMDA and dopamine 2 receptors have been shown to have an effect on cathodal stimulation.

administration of carbamazepine, a Na^+ channel blocker, selectively eliminated the short-lasting after-effects of anodal tDCS. This result is in accordance with early animal studies demonstrating that anodal tDCS involves depolarization of the neuronal membrane. A similar result was obtained for the Ca^{2+} channel blocker flunarizine (Nitsche *et al.* 2003). The fact that these voltage-dependent drugs had no effect on cathodal stimulation is perhaps not surprising since the hyperpolarization that occurs with cathodal tDCS already results in inactivation of the Na^+ and Ca^{2+} channels.

Taking the studies demonstrating changes in TMS, but not TES evoked MEPs, the functional imaging studies and the new data on intermuscular coherence it is becoming increasingly evident that the intra-cortical networks are predominantly affected by the actions of tDCS. In addition to establishing the basis of tDCS as a potentially useful therapeutic method, these mechanistic insights may also allow tDCS to be used as a diagnostic tool.

Acknowledgements

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Jonathan A Norton[1,2]
Hollie A Power[1]
K Ming Chan[1,3]
[1]Centre for Neuroscience,
[2]Department of Surgery and
[3]Division of Physical Medicine and Rehabilitation, University of Alberta, Edmonton, Alberta, Canada

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Toothbrush not terminology

As mentioned in *Physiology News* **66**, 25, The Society Minutes for the 1954 Meeting at Mill Hill noted that in a discussion of terminology for the autonomic nervous system, Bernard Katz had proposed 'sympathetic' and 'unsympathetic' as alternatives to the terms 'orthosympathetic' and 'parasympathetic' suggested by RC Garry and JS Gilespie.

Katz took up the question of nomenclature again in his Sherrington Lectures in which he said:

'Controversies about words, like arguments about priority, are dominated by emotion, and I well remember W Feldberg's dictum, namely that there is a type of scientist who, if given the choice, would rather use his colleague's toothbrush than his terminology.'

Ann Silver
Cambridge, UK

Systems neuroscience workshop at the Marine Biological Association

In September 2007 a practical workshop, *Systems Neuroscience*, was run during the Plymouth Microelectrode Techniques Workshop at the Marine Biological Association.

The workshop taught *in vivo* whole–cell recordings from neurons in different modalities. It took place during the second week of the traditional 2 week workshop on electrophysiological techniques, with a separate experimental and lecture programme open to students attending both workshops. The students were post-doctoral researchers and lab heads from laboratories that are using or planning to use these methods.

The workshop was coordinated by Troy Margrie and colleagues Ede Rancz and Alex Arenz from University College London.

The first lecture entitled *The barrel cortex* was given by Bert Sakmann from MPI Heidelberg and the additional neuroscience lectures by Tom Mrsic-Flogel, Damian Hayden-Wallace, Jim Donnett, Kate Jeffrey, Ole Paulsen, Tim Bliss, Albert Lee and David McAlpine. The Microelectrode Techniques Workshop is supported by the Physiological Society.

David Ogden

Bert Sakmann lecturing on *The barrel cortex* in the Common Room of the MBA, Plymouth during the Systems Neuroscience and Microelectrode Techniques Workshops.

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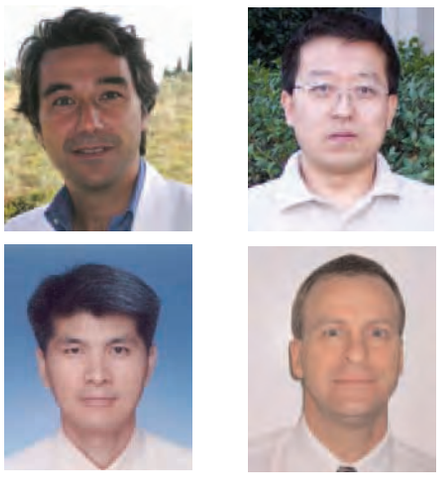
A starring role for astrocytes

Recent evidence continues to re-cast the role of astrocytes in brain function. Astrocytes now appear to express a rich repertoire of signalling mechanisms, can respond to neuronal signals and rapidly signal back to neurons. The recent work of Stephen Traynelis and his colleagues has further emphasized the ability of astrocytic receptors to control excitatory synaptic transmission. Thus these cells have emerged as active participants in brain function



Guido Mannaioni (top, left), Hongjie Yuan (top, right), Justin Lee (above, left) and Stephen Traynelis.

As recently as two decades ago, the primary function of astrocytes was still sometimes mistakenly described as only a supportive matrix for the brain's neurones. Although the word astrocyte means 'star' shaped cell, astrocytes were certainly not thought to play a starring role in central nervous system function at that time. Rather, they were typically assigned a number of supportive and nutritive roles. Over the years, this perception has gradually shifted. Today (more in line with their name), astrocytes appear to take part as primary actors in the regulation of synaptic transmission, a process known to be crucial to the biological computations that underlie thought and perception. Astrocytes can respond to neurotransmitters used in synaptic transmission, clear neurotransmitters from the extracellular space to terminate synaptic signaling, and fine-tune the strength of connections through a variety of different mechanisms. Thus, there is now clear appreciation of the more active and important roles being considered for astrocytes.

The first clue about the communication between astrocytes and neurones was noted in the 1980s when it was found that astrocytes could respond to the chemical signals sent by neurones. Astrocytes express on their cell membrane a large number of neurotransmitter receptors, and these can be activated by neurotramsitters released from neurones. A major step forward occurred in 1994 when Parpura and co-workers showed for the first time that astrocytes were able to signal back to neurones (Parpura *et al*. 1994). Indeed, when single astrocytes were directly stimulated to increase internal calcium and release glutamate, calcium levels of adjacent neurones were increased. Since this discovery, multiple lines of experimentation have defined numerous examples of neurone-astrocyte and astrocyte-neurone communication. However, the molecular mechanisms by which neurone-astrocyte communication takes place as well as its specific role in physiology and/or pathology remain an active topic of investigation. One particularly interesting set of results suggest that G-protein-coupled receptors on the cell surface of astrocytes can stimulate release of Ca^{2+} from intracellular storage sites. Several lines of evidence suggest that the subsequent elevation of intracellular Ca^{2+} levels can trigger release of the neurotransmitter glutamate from astrocytes by a number of different processes (e.g. Parpura *et al*. 1994; Bezzi *et al*. 1998; Araque *et al*. 2000). Glutamate released in this manner is estimated to reach concentrations between 1-6 micromolar, enough to activate neuronal glutamate receptors and influence neuronal function (Lee *et al*. 2007).

Even though the Ca^{2+}-dependent release of glutamate from astrocytes is now a well-documented phenomenon, both the mechanism and physiological roles are still debated. Two classes of mechanisms that have been proposed for astrocytic glutamate release include regulated vesicle exocytosis and channel-mediated glutamate release. In the first mechanism, glutamate is hypothesized to be packaged into vesicles that undergo exocytosis following an increase in intracellular Ca^{2+}. Channel-mediated glutamate release is thought to involve glutamate permeation through channels that open in response to various stimuli.

A number of studies have suggested that glutamate released from astrocytes is capable of activating ionotropic or metabotropic glutamate receptors on neurones. Furthermore, in a recent report, activation of neuronal G-protein coupled metabotropic glutamate receptors by astrocytic glutamate release has been proposed to potentiate NMDA receptor function (Wirkner *et al*. 2007). This is supported by recent findings from our lab (Lee *et al*. 2007). Furthermore, the low level activation of NMDA receptors that we report appears to potentiate synaptic NMDA receptor function by a Mg^{2+}-dependent mechanism rather than intra-neuronal post-translational modification. By using a sensitive bio-detector of glutamate release, we demonstrate that activation of P2Y purinergic receptors, bradykinin receptors, and protease activated receptors (PARs) all stimulate glutamate release from cultured or acutely dissociated astrocytes (Fig. 1*A*, *B*). We chose protease activated receptor PAR1 as a model system to study in depth because of favorable pharmacological and molecular tools, its prominent expression in

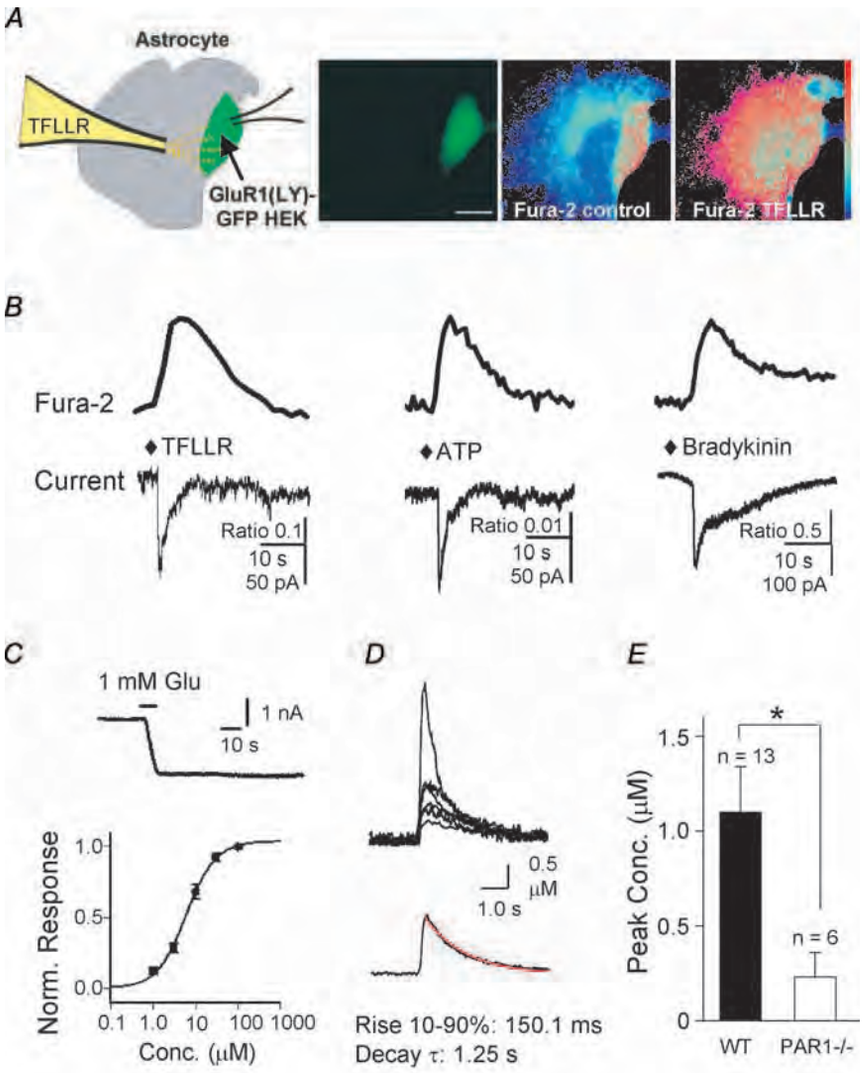


Figure 1. Use of GluR1(L497Y) transfected HEK cells as biosensors for astrocytic glutamate release.

A, A schematic illustrating experimental setup is shown together with GFP fluorescent image of astrocyte – GluR1(L497Y)/GFP transfected HEK cell co-culture (left two panels). The right two panels show the ratio image (510 nm emission; 340 nm/380 nm excitation) of Fura2-AM loaded co-cultures before and after brief (<1 sec) pressure-application of the PAR1-selective agonist peptide TFLLR (500 μM in pipette; EC_{50} 10μM). Calibration bar is 20 μm.

B, Quantification of the fluorescence increase in response to brief (<1 sec) pressure application of 500 μM TFLLR, 300 μM ATP, and 180 μM bradykinin from a pipette in a wild type astrocyte (upper traces) recorded together with the inward current induced in an adjacent GluR1(L497Y)-transfected HEK cell (lower traces).

C, The current response to pressure application of TFLLR was converted to concentration using the dose response relationship and maximal current response of the GluR1 (L497Y) transfected HEK cell determined at the end of the experiment. EC50 value for glutamate activation of GluR1 (L497Y) in transfected HEK cells was 6.1 μM (Hill slope 1.3).

D, Concentration responses from 7 cells are shown superimposed (upper panel) and below as an average (lower panel).

E, A summary is shown for peak glutamate concentration responses determined from HEK cells expressing the non-desensitizing glutamate receptor GluR1 (L497Y) to brief application of the PAR1-selective agonist TFLLR onto cultured astrocytes from wild type mice (WT; 1.1 ± 0.24 μM) and mice lacking PAR1 (PAR1-/-: 0.23 ± 0.13 μM, * $p < 0.05$, unpaired t-test). Modified from Lee *et al*. 2007.

astrocytes, and its high relevance to neuropathological processes. Astrocytic PAR1-mediated glutamate release in vitro is Ca^{2+}- dependent and activates NMDA receptors on adjacent neurones in astrocyte-neurone co-cultures. Activation of astrocytic PAR1 in hippocampal slices evokes an APV-sensitive inward current and causes APV- sensitive neuronal depolarization in CA1 neurones. PAR1 activation enhances the NMDA receptor-mediated component of synaptic miniature EPSCs recorded under voltage clamp, evoked EPSCs under voltage clamp, and evoked EPSPs under current clamp. Magnesium is a divalent ion that is capable of blocking neuronal NMDA receptors at resting membrane potential, and all forms of potentiation are Mg^{2+}-dependent. The data described in this paper suggest that any potential neuronal depolarization mediated by dendritic NMDA receptors in response to astrocytic glutamate release, regardless of the mechanism of release, may be capable of reducing Mg^{2+}-dependent block and potentiating the NMDA receptor component of EPSPs. A large number of G-protein-coupled receptors are coupled to release of intracellular Ca^{2+} from internal stores through the Gαq/11 signalling pathway. These receptors are expressed by mammalian astrocytes, and these results suggest that many of these additional receptors might be able to engage the proposed mechanisms. However, a recent study showed transgenic astrocyte-targeted expression of a peripheral G-protein-coupled receptor that mediates Ca^{2+} signaling did not detectably alter neuronal function. These data suggest that Ca^{2+} signalling in astrocytes might not be involved in synaptic modulation, and also raise a caveat regarding the transfer of conclusions reached from experiments involving activation of one astrocytic G-protein coupled receptor to other G-protein coupled receptors (Fiacco *et al*. 2007).

One important implication of our recent experiments (Lee *et al*. 2007)

is that the level of glutamate estimated to be released from astrocytes (~1-6 μM; Fig. 1*C*, *D*, *E*) following activation of G-protein-coupled protease activated receptors is much lower than that in conventional neuronal synapses. Intra-cleft glutamate has been estimated to reach 1 mM during vesicular release (Clements *et al*. 1992), nearly a thousand times higher than the levels we estimate for astrocytic glutamate release. Even if our estimation of glutamate release was off by several fold, the extracellular concentration still would be sufficient to activate NMDA receptors, but insufficient to activate AMPA receptors. Another feature of our results is that we find different G-protein coupled receptors with similar whole cell Ca^{2+} signalling (Fig 2) mediate different levels of glutamate release. For example, activation of P2Y G-protein-coupled receptors release enough glutamate (estimated peak of 6 μM) to cause significant activation of group I metabotropic glutamate receptors (EC_{50} 10 μM), which can potentiate NMDA receptor responses (Wirkner *et al*. 2007). By contrast, the release of 1 μM glutamate by protease-activated receptor-1 is predicted to cause little mGluR1 activation, even though this level can trigger localized postsynaptic depolarizations. Thus, there may be mechanisms that render compartmentalization and specificity for astrocytic G-protein coupled receptor signalling to neurones.

In the last decade a watershed event has been the acceptance that astrocyte-neuronal communication can take place by many mechanisms, including glutamate release from astrocytes. Our data suggest that this can provide a unique mechanism of NMDA receptor potentiation via relief of Mg^{2+} block. This mechanism may reflect spine head depolarization and consequent reduction of NMDA receptor Mg^{2+} block during subsequent synaptic currents (Fig. 2). Our study provides compelling evidence that astrocytes not only remove synaptically released glutamate, but also actively release glutamate in a Ca^{2+}-dependent fashion to shape the synaptic NMDA responses at nearby synapses. Furthermore, the mechanisms described here are most likely to be shared by a wide range of astrocytic receptors that can elevate intracellular Ca^{2+}. Perhaps most importantly, mechanisms within astrocytes could be potential targets for new therapies to alleviate cognitive and muscle-control deficits for people with brain or spinal cord damage. Thus, true to its form, a star-shaped brain cell may finally be ready to play a starring role in modulation of synaptic transmission.

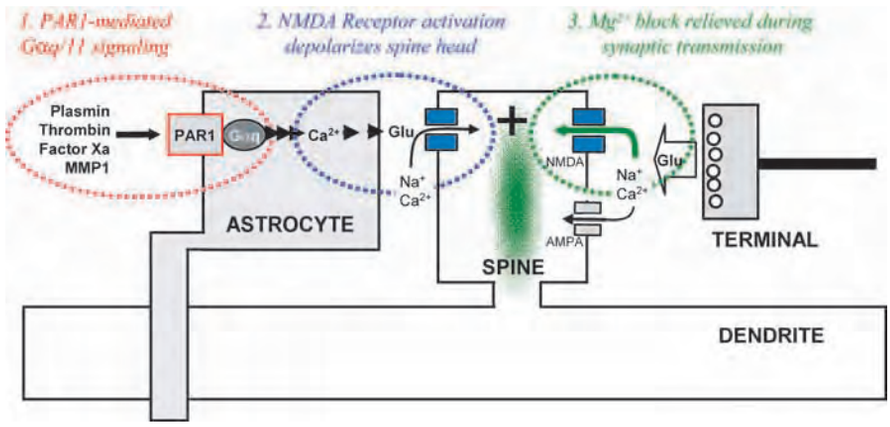


Figure 2. Mechanisms for potentiation of synaptic NMDA receptor function by astrocytic PAR1 activation. The diagram illustrates how PAR1 activation in astrocytes could subsequently lead to potentiation of synaptic NMDA receptor responses secondary to glutamate-mediated spine head depolarization (green) and reduction in Mg^{2+} block of synaptic NMDA receptors. Modified from Lee *et al*. 2007.

Guido Mannaioni[1]
Hongjie Yuan[2]
C Justin Lee[3]
Stephen F Traynelis[2]
[1]Department of Pharmacology, University of Florence, Florence, Italy
[2]Department of Pharmacology, Emory University School of Medicine, Atlanta, GA, USA and [3]Center for Neural Science, Division of Life Sciences, Korea Institute of Science and Technology, Seoul Korea.

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Physiology of an athlete

An open day for local schools and the general public at the University of Essex, Colchester on Friday 4 April, aims to educate, promote and excite families about physical activity and the effect it has on the body and enhance learning for A-level and GCSE in science and physical education. Sponsored by The Physiological Society. More information from ebell@physoc.org

Lack of a role for arterial chemoreceptors in the breakpoint of breath-holding

Oxygen levels in the blood influence breath-hold duration, yet the peripheral chemoreceptors that detect arterial hypoxia appear to have little or no role in determining the breakpoint of breath-holding. Debate about this paradox may have eclipsed another important feature of the breakpoint mechanism

Michael Parkes.

It is a truism that the longer you hold your breath, the lower the partial pressure of oxygen in arterial blood (PaO_2) falls and the higher that of carbon dioxide ($PaCO_2$) rises. It is also well established that breath-hold duration can be almost doubled by preoxygenation and almost halved by previously breathing hypoxic gas mixtures (Parkes, 2006). Since aortic arterial chemoreceptors make no demonstrable contribution to breathing in humans (Guz *et al.* 1966a; Lugliani *et al.* 1971), the carotid chemoreceptors are the only known means of detecting $Pa0_2$ that might influence respiratory control. For this reason there has always been a determination to implicate carotid arterial chemoreceptors in the mechanism explaining the break-point of breath-holding. This is despite the following evidence that they have little or no role!

First, if the carotid chemoreceptors and $Pa0_2$ were crucial in controlling the breakpoint, it would be simplest to expect the PaO_2 at breakpoint to be constant, i.e. a PaO_2 threshold should exist beyond which breath-holding is impossible. PaO_2 is normally around 100 mmHg in eupnea. The mean PaO_2 at breakpoint is typically 62 ±4 mmHg for breath-holds from maximal lung inflation with air (Lin *et al.* 1974). This low PaO_2 at breakpoint, however, is not constant. A breakpoint still occurs for breath-holds from maximal inflation with 100% O_2, even though the PaO_2 at breakpoint (Lin *et al.* 1974) is remarkably higher (553 ±16 mmHg). Conversely, following maximal inflation with hypoxic gas mixtures, the PaO_2 at breakpoint is much lower (24-33 mmHg) than usually seen at breakpoint (Ferris *et al.* 1946).

Secondly, it cannot even be the case that under some of these conditions there is a reinforcing stimulus to carotid chemoreceptors from the $PaCO_2$. The $PaCO_2$ at breakpoint is not constant either (Parkes, 2006). A breakpoint still occurs even if humans breath-hold from low $PaCO_2$ levels (following hyperventilation and in a high oxygen mixture with maximum inflation) and blood gas levels at such breakpoints can be remarkably benign (Cooper *et al.* 2003; Parkes, 2006).

Thirdly, if the carotid chemo-receptors were crucial in controlling the breakpoint, indefinite breath-holding (until unconsciousness) should be possible following bilateral carotid body resection. Such bilateral destruction of the carotid chemoreceptor afferents was originally performed to attempt to treat asthma and results in failure to increase breathing in 12% hypoxia and to respond to hypercapnia via peripheral chemoreceptors (Davidson *et al.* 1974; Gross *et al.* 1976). Yet such indefinite breath-holding is not seen. Fig. 1 shows that their breakpoints persist. There is no difference in mean breath-hold duration *vs.* intact controls following maximal inflation with 100% O_2. Fig.1 nevertheless does show that mean breath-hold duration is 54–65% longer in denervated patients following maximal inflation with either air or hypoxic gas mixtures. This prolongation has never been explained. One interpretation is that it merely represents a difference between the healthy controls and these severe asthmatics, since breath-hold duration was not measured before operation. (Prolonged breath-hold duration was not seen, however, in other asthmatics). Thus carotid chemo-receptors may have no role in

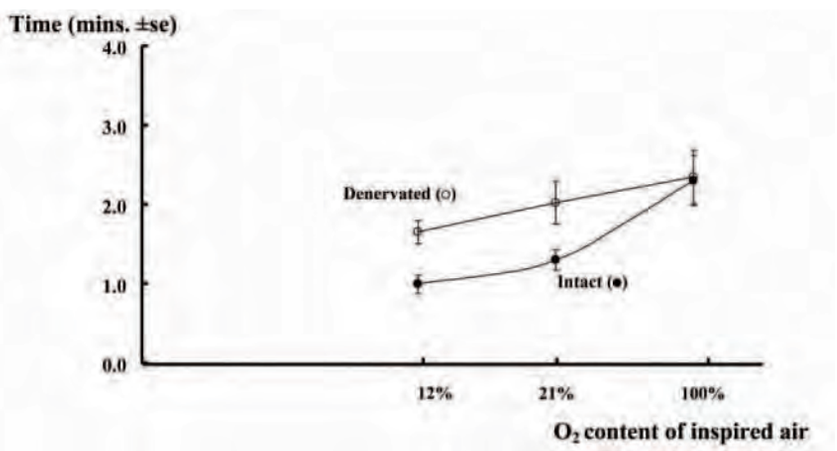

Figure 1. Effects of bilateral carotid body denervation on mean breath-hold duration. Seven intact subjects breath-holding at inspiratory capacity from 100%, 21% & 12% O_2 (joined by lines) *vs.* five denervated subjects [from Gross *et al.* (1976); Parkes (2006), with permission from the American Physiological Society and *Experimental Physiology*]. Note denervated subjects still have a breakpoint. Although their mean breath-hold duration with 100% O_2 is not prolonged, their mean durations with 21 or 12% O_2 are 54-65% longer [see also Davidson *et al.* (1974)].

the breakpoint. Another explanation is that the absence of chemoreceptor afferents contributes to a lessening of the sensation of discomfort that accompanies breath-holding in air and hypoxia. Thus carotid chemoreceptors may make some little contribution to the duration and hence to the breakpoint. These differences have never been resolved and the experiments may not be repeatable with modern ethical concerns.

The reason for publicising this debate about carotid chemoreceptors is that it may have eclipsed one further, even older experiment that may be important for our understanding of the breakpoint mechanism.
In 1966–1970 Noble *et al.* (1970) infiltrated local anaesthetic into regions around the glossopharyngeal (IX) and vagus (X) nerves bilaterally in three normal, conscious subjects. Adequate cranial nerve blockade was established by inability to swallow (X & IX), almost complete absence of phonation (X), development of a bovine cough (X), absence of cough to ammonia (X) but no paralysis of the tongue (XII). Breath-holds were from the end of a normal lung deflation and apparently from 100% O_2. Fig. 2 shows that mean breath-hold duration was almost trebled. The absolute durations are also remarkable because breath-holds were only from end lung deflation (whereas those in Fig. 1 were from maximum lung inflation). It is also remarkable that breath-holding even remains possible without motor control of the glottis.

These experiments have been eclipsed because of the possibility that the prolongation was explained by blockade of carotid chemoreceptor afferents. But we now know from Fig. 1 that carotid nerve resection has no effect on breath-hold duration from maximal inflation with 100% O_2. So the prolongation must be explained by something else. One possibility is that it was due to blockade of the pulmonary afferents in the vagus nerve that detect pulmonary inflation, deflation or irritation. But this cannot be the explanation either, because breath-hold duration is no different in patients with pulmonary vagus denervation (i.e. with lung transplantation) *vs.* either intact controls (Harty *et al.* 1996) or patients with heart transplantation (Flume *et al.* 1996). So apparently there remains another unidentified afferent in the vagus (or glossopharyngeal) nerves that makes an important contribution to the breakpoint. Of course Noble *et al.* (1970) only describe three subjects. No-one has ever confirmed their results (certainly with modern ethical concerns they never will!). Moreover, even this unidentified afferent does not provide a complete explanation, because breath-hold duration was only prolonged. Subjects still could not breath-hold to unconsciousness.

So how can it be that breath-hold duration is so affected by oxygen levels, yet the only chemoreceptors known to detect arterial hypoxia have little or no role in the breakpoint mechanism?

Michael J Parkes
School of Sport & Exercise Sciences, University of Birmingham, Birmingham, UK

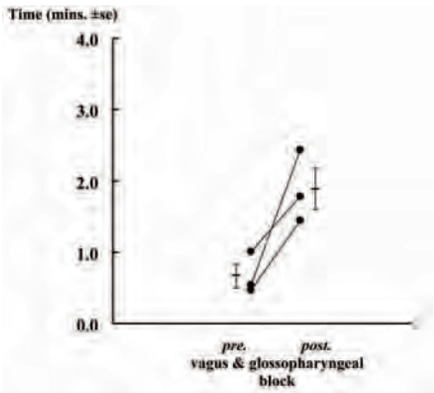

Figure 2. Prolongation of breath-hold duration by bilateral vagus and glossopharyngeal nerve block. Three normal subjects breath-holding from the end of a normal deflation (at FRC) and apparently from 100% O_2 (Guz, 1966; Guz *et al.* 1966b; Noble *et al.* 1970). Circles joined by lines indicate individual subjects with the mean ±se for each pre and post block condition indicated as horizontal bars [from Noble *et al.* (1970); Parkes (2006) with permission from the Novartis Foundation and *Experimental Physiology*] (see also Guz, 1966; Guz *et al.* 1966b).

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Sydney Ringer's life and work commemorated at Lastingham

Sydney Ringer (above), with the Italian stained glass which he commissioned visible in the windows behind the altar; Alastair Ferguson, David Miller, David Eisner and Neil Davidson (below, top); Dafydd Walters unveiled a plaque and toasted Ringer's memory (below, bottom).

At last, Sydney Ringer is properly commemorated at St Mary's Church, Lastingham, North Yorkshire, where he was buried nearly 100 years ago. Ringer was not recorded in much detail in the village, despite having funded the major restoration of the ancient church in 1879. Furthermore, with his family, he had contributed significantly to public life in the area where they had a holiday home for 40 years. On 27 October, at the invitation of the Friends of Lastingham, I gave the 4th annual *Lastingham Lecture*, with David Eisner as the supporting act. We spoke from the aisle, next to St Mary's pulpit, if not actually in it; a first for us both. Dafydd Walters unveiled a plaque and the recently published booklet on Ringer's life* was launched. We were supported by the presence of Clive and Margaret Orchard, Sue Wray, Matthew Lancaster, Sandra Jones and Linda Rimmer as well as Dafydd's wife and mine, as we sought to show Lastingham's villagers why The Society has a serious regard for their old parishioner and benefactor.

A large, paying audience of local people, plus the delegation of physiologists, filled St Mary's. My lecture emphasised Ringer's life and times, especially those in Lastingham, but also illustrated the reasons for his being celebrated in physiology, pharmacology and medicine. David Eisner gave a splendid insight into how Ringer's foundation of the 'calcium' story underpins modern understanding of the life of our body cells 'from conception to death'. Whether the lay public felt encouraged to take calcium pills, or the opposite, was a discussion point later. Dafydd Walters proposed a toast to Ringer's memory as he unveiled a plaque near the South Porch. The new brass plaque, sponsored by The Society, twins one that names Ringer's daughter, Annie, whose tragically early death had prompted the 1879 restoration. (Regrettably, my discovery that Ringer was born in 1836 – rather than 1835 as his gravestone and other sources have it – was made after the plaque had been engraved.)

The evening continued in the Village Hall, built to be the School House in memory of Ringer's mother-in-law and, again, largely at his own expense. The splendid Yorkshire 'otpot supper was a sell-out event, greatly enjoyed by about 60 diners; the Blacksmith's Arms pub kindly sent over jugs of beer as lubricant. Remembering a great scientist and physician can have unexpected bonuses. The phalanx of physiologists toasted their generous hosts who were led by Neil Davidson, Chairman of the Friends of Lastingham, and the Rev Dr Alastair Ferguson, the vicar.

Visitors to Lastingham, a tourist gem of the North Yorks Moors, can now read a little about Ringer for themselves and, we hope, learn something of the contributions to science and medicine that have kept his name alive, at least amongst physiologists. We can hope that one of the great, early experimentalists in our subject will steadily gain the wider audience that his pioneering discoveries on calcium, physiological saline and the heart really do deserve.

If you have favourite 'fathers' or 'mothers' of physiology, I encourage you to look into their lives and times too. Research and teaching is done by real people; knowing more about the context of their work extends our understanding of what was done and, perhaps, the more elusive 'why'.

David Miller
Glasgow

**A solution for the heart* can be downloaded at www.physoc.org/downloadfiles/RingerBooklet.pdf Paper copies (£1 each) can be obtained from The Society's Publications Office (lrimmer@physoc.org) and will be available at Society meetings. Donations made at St Mary's church for the booklet will help to defray printing costs. David Miller has been awarded the Paton Prize by The Society's History and Archives Committee for this work (see also p. 51).

Sir Andrew Huxley at 90

Sir Andrew Huxley (above); symposium organisers David Trentham (left) and Jonathan Ashmore (below) *(photos by Martin Rosenberg)*.

On 14 November 2007 there was a very well-attended meeting in the AV Hill Lecture Theatre at University College London, organised by Jonathan Ashmore, David Trentham and Roger Woledge to celebrate the 90th birthday of Professor Sir Andrew Huxley, OM FRS and Nobel Laureate in Physiology and Medicine.

The talks illustrated the wide-ranging interests of Sir Andrew's scientific career, starting with nerve conduction. His initial short *Nature* paper with Alan Hodgkin in the summer of 1939 (Hodgkin & Huxley, 1939), published from the Plymouth Marine Biological Laboratory, showed for the first time the positive overshoot of the action potential (Fig. 1) and was a masterpiece of technique and observation. Any scientist at the peak of their career would justly be proud of such an achievement, let alone a 22 year old medical student. The work was then interrupted by the outbreak of WW2, and the full description of the pre-War Plymouth experiments, with detailed methodology, had to wait until the October 1945 *J Physiol*: 'the experiments ... were made in 1939 and the bulk of the paper was written in 1940' (Hodgkin & Huxley, 1945).

The definitive quantitative analysis of nerve conduction followed some years later in 1952 in the classic series of Hodgkin-Huxley papers published in *J Physiol* (**116.4** and **117.4**). This *tour de force* led eventually to the award of the Nobel Prize for 1963 (with Hodgkin and coupled with John Eccles' work on nerve synapses).

The morning ended with an interesting and illuminating overview of the physiology of hearing given by Robert Fettiplace, shortly to take over as Professor of Physiology at Cambridge University. Sir Andrew made a theoretical contribution to that field that has proved important in subsequent years (Huxley, 1969).

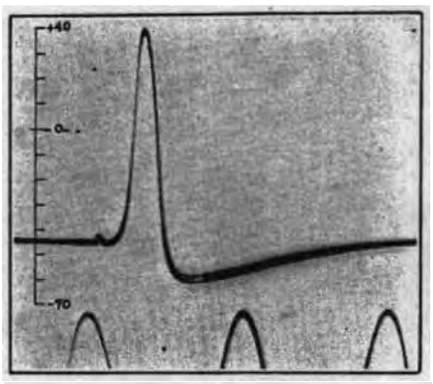

Fig. 2.
ACTION POTENTIAL RECORDED BETWEEN INSIDE AND OUTSIDE OF AXON. TIME MARKER, 500 CYCLES/SEC. THE VERTICAL SCALE INDICATES THE POTENTIAL OF THE INTERNAL ELECTRODE IN MILLIVOLTS, THE SEA WATER OUTSIDE BEING TAKEN AT ZERO POTENTIAL.

Figure 1. (from Hodgkin & Huxley, 1939).

After lunch the meeting concentrated on muscle contraction, which Huxley turned to in 1952, partly because he started to give the Cambridge lectures on the subject when his friend David Hill (DK Hill, son of AV) left for London. Sir Andrew is now the unchallenged doyen of muscle physiologists. With Rolf Niedergerke he developed interference-microscope techniques to examine the behaviour of striated muscle A- and I- bands during contraction, and this was the basis of another classic paper in *Nature* (Huxley & Niedergerke, 1954), one of the pair of papers that established the sliding-filament model. [The other paper of the pair, published back to back, was by Hugh Huxley and Jean Hanson using phase-

Participants at the international symposium honouring Sir Andrew Huxley OM, FRS, Nobel Laureate, on the occasion of his 90th birthday (*photo by Neal Cramphorn*)

Gerald Elliott (left) and Richard Tregear catch up; symposium participants (right) (*photos by Neal Cramphorn*). More images on the inside front cover.

contrast microscopy on single muscle myofibrils (Huxley & Hanson, 1954)].

The afternoon programme began with a movie made by Andrew Huxley in 1965, *Muscular contraction under the microscope*. This was Sir Andrew in his prime and his presence and distinction were commanding. Some years before this he published his seminal review article on the cross-bridge mechanism in muscle contraction (Huxley, 1957), setting out a mathematical model that has been hugely influential, and indeed dominant, in the field to this day.

After the movie Malcolm Irving, Anne Houdusse and Justin Molloy described current experimental work that has illuminated understanding of the workings of the muscle cross-bridges. There were also some interesting personal accounts by Vincenzo Lombardi, Yale Goldman and Bob Simmons of what it was like to work closely with 'Prof'. Bob Simmons suggested that if there were to be an SI unit for excellence in scientific research it should be called an 'Andrew Huxley'.

For me, the true highlight of the meeting came at the closing reception in the Jeremy Bentham Room when wine was served and Sir Andrew gave his own personal account of his scientific life. This was truly the stuff of scientific history and we hear such accounts too rarely. He told us how, as a boy at school, he had been mechanically minded, interested in how things worked and in mechanisms in general, and had been inspired by his physics teacher. Starting the Science Tripos at Cambridge he had read physics, chemistry and maths, intending to become an engineer. However, needing a fourth subject he had picked on physiology and quickly become fascinated. He then began a clinical degree, which at the time was the gateway to professional physiology, but at the outset of the Blitz he had gone into operational research in gunnery. In parenthesis, he worked in the Admiralty in a section headed by the physicist Patrick Blackett, later Nobel Laureate in Physics and Lord Blackett of Chelsea. It has been said, though I forget by whom, that the young Andrew looked very dashing in his naval officer's uniform! Blackett was later President of the Royal Society (1965-1970), succeeded by Alan Hodgkin (1970-1975) and later by Andrew Huxley (1980-1985).

Back in Cambridge after the war Andrew Huxley was a Fellow of Trinity, teaching and carrying on his research. In 1960 he was offered and accepted the Chair of Physiology at University College London. He had, he said, consulted someone important (AV Hill, as I remember it) and had been told 'You should start in Cambridge and perhaps finish there, but mid career you should work in another environment'. Sir Andrew did end up in Cambridge; after his distinguished period as President of the Royal Society he was Master of Trinity, and is now Senior Fellow of the College. He is also a member of the Order of Merit and was recently pictured in the newspapers with the Queen and the limited membership of that outstanding Order, chosen personally by the Sovereign.

The study of muscle exemplifies beautifully the different approaches that can be used to search for information about molecular mechanism; physiological, biochemical, biophysical and most recently 'molecular structural'. When I think about muscle contraction I often recall a metaphor from a hymn that I used to sing at school assembly 60 years ago: *' each sees one colour of the rainbow light; we are not perfect till we find the seven '*. (Poignantly, George Matheson, who wrote those words, became blind in adulthood). Personally I retain doubts that the *total* spectrum of how muscles produce tension has yet been illuminated. However, there can be absolutely no doubt that the superb experimental work and the great mechanical insight of Sir Andrew has contributed more to the vision as we now have it than any other living scientist has done.

The day closed with a dinner for Sir Andrew, the speakers and other friends.

Gerald Elliott
Nuffield Laboratory of Ophthalmology, University of Oxford

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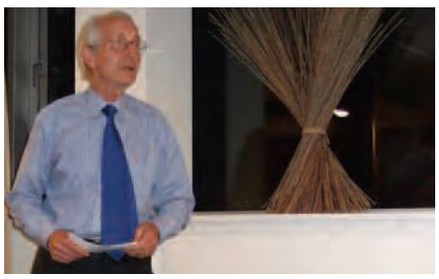
Pre-emeritus symposium for Richard Olver

The Physiological Society generously supported a pre-emeritus symposium for Richard Olver in Dundee in September to celebrate his many contributions to the understanding of ion transport in the developing lung. Rather than focusing on his many achievements, Richard, with characteristic modesty, wanted the symposium to reflect on 40 years of research into pulmonary ion transport [he later explained that it was only 33 years since he and Leonard Strang first reported active ion transport in the mammalian lung in *The Journal of Physiology* (Olver & Strang, 1974) but 40 years since the initial groundwork had been laid at UCL]. My own task was to ensure that the delegate list and speakers were reflective of his wish and in the event, around 50 scientists contributed to this meeting. The feedback from the delegates was overwhelmingly positive.

Prem Kumar started proceedings with an overview of the role of The Society in fostering such events and then proceeded to briefly examine the Olver & Strang paper, commenting that the understatement of its important conclusions was very different to current practice. The symposium then proceeded with a lively atmosphere of debate, sometimes with great controversy when treatment approaches to the disordered sodium transport in cystic fibrosis were discussed (but more of that later).

Although sodium and chloride always remained centre stage, a related theme played an important role, namely signalling pathways affecting lung development with many discussions on topics as diverse as stem cells, lineage branch points, tracheal versus alveolar morphogenesis and of course, ion channel regulation itself. Contributions were received on such topics from the USA, Switzerland and EU. See the full list of topics at www.dundee.ac.uk/mchs/ndpk .

The aim of the first morning was to update the delegates on new ideas in the control of epithelial sodium and chloride transport by a pleotropic protein kinase, CK2 (formerly casein kinase 2). Karl Kunzelmann (Germany) focused on the role of CK2 in the expression and function of the epithelial sodium channel (ENaC) and Lorenzo Pinna (Italy) provided new data on the complex interaction between CK2 and the nucleotide binding domain 1 in CFTR. This was followed with an overview from Robert Clarke (UK) on epithelial stem cell lineages together with a functional review by Jeff Whitsett (USA) of the processes controlling lung development. Jeff had given a talk on the previous day where he drew on parallels between developmental pathways and their reactivation during oncogenesis in adult life and in his second talk provided new insight into disorders of lung development using mouse models.



Richard Olver makes his virtuoso speech, combining his roles as a scientist and clinician (above); symposium delegates (below).

To enliven post-prandial proceedings in the afternoon, Ray Frizzell (USA) returned to the ENaC topic to review the regulation of that channel with the remit to stir the ingredients for the pro-con debate. This debate was designed to test the hypothesis that drug-based inhibition of the recognised excess sodium channel activity found in cystic fibrosis airway epithelia would lead to therapeutic benefit. It was immediately clear that Jeff Whitsett and Ray Frizzell, who chaired the debate, would have their work cut out in controlling the protagonists (Marcus Mall (Germany) versus Steve Ballard (USA) and Fred Becq (France) versus Bob Scholte (Netherlands)). Rapidly, opinion became as polarised as the epithelium in question with apical and basolateral camps forming segregated views of remarkable intransigence. Bob Scholte was in his element and vigorously opposed the motion. Ballard harnessed his considerable native southern US charm but was more circumspect in his glandular view of CF pathogenesis whilst trying to see the other point of view. Mall outlined broad strategies from his animal

model data but the house felt that in the absence of a true CF animal model, the interpretation of the protective effect against lung damage of sodium channel inhibition remained unproven. GB Shaw once said that progress is only made by those who disagree but, despite the great man's views, no clear consensus emerged from the debate other than the feeling that such pharmaco-therapy, whether directed against proteases targeting the channel or against the channel pore was well worth pursuing even though the exact end points to gauge success remained unclear.

Delegates were now ready for an hour of reminiscences, both humorous and serious, covering Richard Olver's career. The early Olver years *in Londinium* were covered by Dafydd Walters and Robert Boyd (UK), who focused on his days at University College. As with many things in science, the discovery that adrenaline could stimulate lung liquid absorption came about by accident when a beta-adrenoceptor agonist was administered for a completely different reason by Dafydd. But, as they say, chance favours the prepared mind and the rest is history. The middle Olver years were covered by a double act that would have had Laurel and Hardy laughing in their seats when Debbie Baines and Harry McArdle (UK) took stage. They described the embryogenesis of the Department of Child Health with caricatures of such luminaries as Paul Kemp (*in absentio*, sadly) and the supportive roles played by other members of the University. Finally, Stuart Wilson described the conjoinment of Child Health in its initial configuration as the Tayside Institute of Child Health (TICH) to its fusion to create a combined Obstetric and Paediatric research entity, Maternal and Child Health Sciences.

By this stage of the evening, delegates had earned their supper, during which Sir Robert Boyd and the Principal of the University of Dundee, Sir Alan Langlands, made impromptu speeches to complement Richard's earlier virtuoso speech that had combined his roles as a scientist and a clinician with a hitherto hidden talent for comedy. Delegates retired to the bar after dinner, but were ready bright and early the following morning for the second feast of science. This began in exemplary fashion when Markus Affolter (Switzerland) gave a masterful overview of how to make a trachea from scratch (and a few genes) albeit, at this stage of understanding, focusing on fly tracheal morphology. This was followed by further analysis of mucus and fluid secretion in gland function in large airways from Steve Ballard. The picture was completed by Mike Gray (UK) who agreed to move away from his beloved pancreatic duct to show us how the airway was really a pancreas in disguise because of the vital role it plays in bicarbonate secretion.

The symposium was naturally rounded off by a return to the sodium theme. The final talks focused on ENaC and its potential role in airway diseases and it seemed fitting for this section to focus on the latest developments in thinking about the roles of cell energy, intracellular kinase mediated pathways and a look into the future. A sterling job was done by Debbie Baines, Marcus Mall, Stuart Wilson and David Sheppard (UK) to set up the close, with a look to the future in a combined presentation from Ray Frizzell and Margarida Amaral (Portugal). All in all much fun was had. Richard, now emeritus and shorn of managerial responsibilities, has been spotted in the laboratory much more frequently. So watch this space for more discoveries from the City of Discovery.

In summary, we celebrated 40 years of ion transport research but only concluded that it may take another 40 of the best science to make inroads into disease pathogenesis.

We thank The Physiological Society for their support without which this would not have been possible, and the University of Dundee for their logistic support. We also thank the EU Framework 6 (EuroCareCF, www.eurocarecf.eu) and David Sheppard in particular as the coordinator for supporting the pro-con debate and are grateful to the CF Foundation of the USA for their generous contribution to this event.

Anil Mehta
University of Dundee, Dundee, UK

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Your skills, our future

Students undertaking complementary medicine and adult nursing degrees, along with practitioners and educators from within the industry, attended the *Your skills, our future* conference organised by the London and Counties Society of Physiologists and the University of Central Lancashire (UCLan) at Herons' Reach Hotel in Blackpool. Kay Byatt (Leader, Complementary Medicine Division at UCLan) gave the key note lecture on the state of play regarding education, research and development of complementary medicine in the UK. Peter Mackereth (Clinical Leader, Christies Hospital) and Miguel Diego (Researcher, Touch Institute, Miami Florida) also gave presentations.

Concurrent sessions allowed delegates to participate in clinical workshops relating to massage, touch and other body work therapies. Delegates came from a diverse range of backgrounds, with varying degrees of clinical capability. Some were therapists with years of clinical experience, whilst others

were students with no clinical skill in massage.

The diverse groups made the practical workshops interesting and nothing could be taken for granted about people's knowledge base. Massage treatments were performed by students from the Northern Institute of Massage and were very well received by delegates.

Student nurses attending the conference (some of whom are pictured on p. 40) thoroughly enjoyed the opportunity to find out more about complementary medicine and commented that the event would help with their studies. Students studying complementary medicine, and especially massage as a therapy, were able to learn about the evidence base for massage and were impressed with the quality of evidence available regarding the measured benefits of massage.

Pauline Stuttard (Senior Lecturer, UCLan) hoped that a similar conference would take place next year and would be open to UCLan students studying in the Nursing Department and Complementary Medicine Unit.

Programming of the neuroendocrine and immune stress responses in early life and their role in health and disease

A workshop was held at Rottnest Island, Perth, Western Australia on 11 and 12 November to discuss current advances in our understanding of the way that alterations in stress responses might be one of the key processes linking early adverse environmental exposures and poor somatic growth with health and disease in adult life. The workshop was sponsored by The Physiological Society and Johnson & Johnson, with over 40 people attending. They were from 13 different countries and represented a

unique mix of disciplines including neuroscientists, psychobiologists, epidemiologists and clinicians.

The major themes were *stress as an exposure*, *stress as a mediator*, and *stress as an outcome* which recognises the way in which maternal stressors affect neuroendocrine development of the fetus which in turn leads to long-term changes in the set-point of adrenocortical (HPA), autonomic and immune function. In adult life these changes may increase the susceptibility to a variety of adult conditions which not only include cardiovascular and metabolic disease but also susceptibility to mental illness.

Discussion centred on the major research problems in this area and applying what has been learnt from animal studies to understand human fetal programming. This is difficult because of substantial species differences in the way these systems work. The assessment of maternal stress has proved to be problematic. Much depends on a woman's recall. However, measures of perceived stress are poorly associated with peripheral physiological measures. To complicate things further, there is very substantial intra-individual variation in the way different mothers respond to different stressors. How maternal stress affects the developing neuroendocrine systems in the fetus is also a challenging problem to assess in viviparous animals because the signals from mother to fetus are imperfectly understood and hard to measure. Although the fetal and infant environments have important modifying effects on the offspring stress response, there is also a significant genetic basis. There is a large body of research indicating that single nucleotide polymorphisms (SNPs) impact on the HPA and autonomic function. However, each SNP only accounts for a small amount of the variance. More recent work has shown that there is epigenetic modification of many components of the system. Epigenetic variation is known to interact with both genetic variation and with the environment experienced during development in determining the eventual phenotype. Finally, studies of the phenomenon are further complicated by the data that gender and age of the offspring appear to have additional modifying effects on the magnitude and nature of the HPA and autonomic response.

The evidence that these systems are important in determining susceptibility to adult disease depends largely on cross-sectional, association studies showing, for example, that measures of vascular function, or glucose homeostasis are related to prevailing glucocorticoid levels or autonomic activity. There are fewer prospective studies but where these have been carried out, the results have been encouraging. There is, however, a need for experimental studies and trial evidence, which will be greatly helped by the development of pharmacological strategies to modify the stress response.

The heterogeneity of stress responses in different individuals described above represents a considerable difficulty. One possible way of getting round this problem is to define categories of physical and psychological symptomatology as recognisable and distinct phenotypes. These have been termed *neuropatterns*. Preliminary data suggest that three common *neuropatterns* are associated with early adversity:

- *Locus coeruleus* hyperactivity, characterised by evidence of anxiety, autonomic activation and

related conditions including PTSD, hypertension and irritable bowel syndrome;
- CRF/PVN hyperactivity with hypercortisolism, depression and the metabolic syndrome;
- Adrenal hypoactivity, characterised by symptoms of burnout, fatigue and fibromyalgia.

This workshop underlined that much of the fundamental biology is not understood. A further key question is whether we will ever be able to intervene usefully. There are, however, a number of primary intervention studies underway. Most of these are nutrition trials and include for example, pregnancy supplementation with vitamins B12, folic acid and vitamin D, use of an omega 3 rich diet and nutritional supplementation of teenagers of low socio-economic status. There are also trials to prevent gestational diabetes by limiting weight gain in pregnancy or encouraging physical activity. The proposed outcomes of these trials are improvements in growth or physiological parameters related to cardiovascular risk and few, if any, are evaluating the effect on neuroendocrine stress responses. However, these additional measures could easily be incorporated in small subsets undergoing the trial.

Interventions to reduce psychosocial stress during pregnancy represent another possibility but are more difficult to carry out. However, many governments are currently introducing measures to improve conditions for pregnant women, for example by allowing more generous maternity leave and increasing the availability of financial help during pregnancy. Again it would be of great interest if the effect of these interventions on neuroendocrine function could be evaluated. In the longer term, however, it is likely that a multifactorial approach may offer the best intervention. An example of this has been pioneered by David Olds showing that targeting poor health behaviours (including diet, smoking and social support) in women of poor economic status resulted in a halving of the rate of offending in their 15 year old offspring.

Fetal neuroendocrine programming is becoming an important area of science in which both basic science and systems physiology is going to play an important role and that progress will depend on collaborations between scientists from different disciplines. An important positive outcome of the workshop was the recognition that the group needs to develop an identity and meet regularly in the future.

David Phillips
University of Southampton, UK
Dirk Hellhammer
University of Trier, Germany

First year bioscience laboratory classes – score gamma?

It is recognised there is a shortage of bioscience graduates with laboratory skills and aptitudes. It was therefore thought worthwhile to discover students' views on the laboratory work they undertook in year 1 of bioscience courses so that changes could be made which might improve the students' view of laboratory work and feed through to later years a student body more interested and involved in laboratory work. In conjunction with AstraZeneca and the British Pharmacological Society, the Centre for Bioscience has therefore surveyed 1st year bioscience students about their views on laboratory classes they were undertaking. Returns from 695 students (70%) in nine UK universities were obtained between February and April 2007. While this was a good response rate, it must be borne in mind that an opinion expressed by say 40 students represents less than 5% of the returns.

Results

Most students preferred the laboratory classes they had experienced at school to those they were experiencing at university (*' very good explanations and demonstrations given; much more help given; a lot more teaching around the subject before the practical and told exactly what to do and why '*).

Although student views were varied, there was clear identification of the best features of university laboratory classes as:

- learning new skills and using new equipment;
- the opportunity for social interaction with students and teachers;
- the function of practicals to illustrate material given in lectures;
- the acquisition of new knowledge through practical classes;
- high interest value of practicals.

Students identified the worst features of university laboratory classes as:

- the length of practicals (*'too long'*);
- the poor organisation (*'always waiting about for stuff'*);
- the associated write-up (*'too time - consuming, too long'*);
- the tedious/boring/repetitive nature of practicals;
- the variable contribution of staff (*' staff were rude if you didn't understand something '*).

Discussion

Overall the data raises concerns that for many students the experience of laboratory work in the first year Is not good and there are some themes which suggest ways forward.

The effectiveness and consistency of staff at all levels teaching the practicals. It is appropriate to ensure staff are competent and able to TEACH (as opposed to just run the practical). The importance students place on knowing people in their class and their teachers and forming friendship networks should be recognised and enabled.

Students find 1st year practicals long, boring and tedious. While appreciating that teaching skills are

important (and valued by students) there should be an additional explicit objective for 1st year practicals – enthusing and interesting the students in laboratory work by ensuring they experience the excitement of discovery.

The issue of organisation in practicals. The students' emphasis on '*waiting around*' for one thing or another. In part this may be an issue of equipment shared between too many students.

We need to address the heavy emphasis students place on equipment (complicated, advanced, better) and get across that equipment is not an end in itself. Repeatedly, students emphasised their interest in equipment, never what it enabled them to do.

The issue of students enjoying practicals at school because they felt more relaxed may come from the greater familiarity they have with the school environment. At the first practical, *everything* and *everybody* is new to students at university.

The magnitude of the transition which students are undergoing from school to university needs to be recognised. As one student said '*it felt like I'd been thrown in at the deep end and without a float*'. We should consider starting in a very supported environment and allow students to make the necessary transitions over a *set* of laboratory classes during semester 1.

We must recognise that 50% of students taking biosciences courses may take employment outside bioscience, let alone involving laboratory work, and courses at university need to provide a good and appropriate experience for ALL students.

Two interesting suggestions emerged which might be areas for development:

'*students should be able to do a lab again until they are satisfied with it*' and '*it would be useful to have a take away example of a perfect experiment for revision purposes*'.

Finally, reporting some very positive comments made:

'*on the whole I love them and find them really useful and always fun to do*' and '*brilliant lab classes with helpful tutors and great instructions. I've learned a lot and enjoyed so much. Thanks*.'

Conclusions

While most students in the biosciences progress to careers not involving practical work, some will become involved in practical studies in education, research and industry. The early experience in university is likely to have profound effects on whether some students see practical science as an attractive and exciting career choice. The survey results suggest ways in which 1st year bioscience practical classes could be more engaging and stimulating and moving from gamma to beta or even alpha.*

Mike Collis
Alan Gibson
King's College, London
Ian Hughes, Gill Sayers
Centre for Bioscience, University of Leeds
Martin Todd
AstraZeneca

* Full results of the survey are available at: ftp://www.bioscience.heacademy.ac.uk/reports/1styearlabs.pdf).

Cystic fibrosis

Latest advances in medical research and implications for patients and their families

This was the first in a new series of Physiological Society external relations events, aiming to discuss the relevance of physiological research to audiences who might not normally attend our meetings. The Society's partner for the event at The Royal Society In London on 19

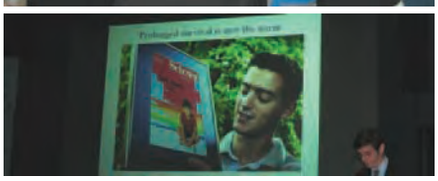
Vicky Cowell and David Sheppard (above) and Mike Gray (below).

November was EuroCareCF, Co-Ordination Action for Research in Cystic Fibrosis, a forum funded by the European Commission's 6th Framework Programme for all individuals working to defeat the disease. Our speakers were Vicky Cowell (the mother of Laura, a cystic fibrosis (CF) patient in her early 20s), Mike Gray (Newcastle University and Deputy Chairman of the Research Advisory Committee of the Cystic Fibrosis Trust), Alastair Innes (Consultant Physician and Director of the Scottish Adult Cystic Fibrosis Service, Western General Hospital, Edinburgh), The Society's President, Ole Petersen (Liverpool University), and David Sheppard (Bristol University, Co-Ordinator of EuroCareCF). The event aimed to explore some of the basic science underlying CF, recent research developments, their likely impact on clinical applications, and the perspective from the point of view of CF patients and their families.

The seminar therefore covered a great deal of ground. Points made that particularly struck me on the day included the history that the disease has been known for a very long time, with old European folklore referring to 'the child that tastes

salty will die', a practical reference to CF patients having a high concentration of salt in their sweat. We now know from Nobel Prize winning research that defective chloride channels in the epithelium are to blame, with the responsible gene (CFTR) having been identified, causing havoc in many key tissues of the body, from the lining of the lungs to pancreatic cells. The clinical symptoms of failure of these core systems are life threatening, the one killing most CF patients being the inability of the lungs to clear themselves of secretions and bacterial infection. Clinical practice has made radical advances in managing the symptoms over the last few decades, greatly extending CF patients' lives, with many of those who would otherwise have died in infancy living for decades into adulthood (median survival now 36 and rising). Tried and tested life saving treatments include physiotherapy to help clear patients' lungs, antibiotics to treat lung and other infections and, in extreme cases, organ transplantation. But this places a heavy burden on patients and their families, requiring many hours of effort each day to manage the various symptoms.

Radical advances in research mean that we can now start to move from managing the symptoms to addressing the underlying condition, for example targeting the action of the mutated relevant gene with novel drugs for ion channel therapy. A long term cure may eventually be effected by manufacturing the healthy version of the gene and transporting it into affected patients' tissues. The vector can pose some challenges, various viruses that infect our respiratory systems could help, but can be blocked by the body's immune response. Non-viral liposome vectors may be less immuno-genic, but have no particular affinity with epithelial surfaces. Manufacture of the gene to be transposed can also raise immuno-genic issues. A gene manufactured by bacteria can be different enough from mammalian DNA for the immune system to



Question time with David Sheppard (top); Alastair Innes (centre); Laura Cowell, born with cystic fibrosis (above).

detect it, and therefore needs modification before use. Manufacture of the gene of the right quality has now been achieved, with the next UK clinical trial in 2009. Potential gene therapies pose particular ethical questions. Regulatory authorities will not permit gene therapies that might be inheritable; treatment of somatic cells is much more acceptable. When to treat patients also raises ethical dilemmas. Older patients have already suffered significant damage, have less to lose, and can give informed consent; whereas babies still have good lungs, with the advantage that successful gene therapy can protect their lungs before damage occurs. But they cannot give consent.

After the science and clinical applications had been discussed, Vicky gave an eye-opening and often hilarious account of life as a CF mum. Her daughter Laura was born with the condition in 1985, with physicians failing to spot the problem for some time. Explanations for Laura's constant crying and failure to put on weight included possible allergy to dairy products. She was lucky that her GP had stayed with a family in Australia with CF, and spotted that Laura was the salty baby of folklore. Vicky said that another good symptom to look for in a CF baby is truly appalling nappies, apparently nothing stinks like it! Eventually the hospitals started to get their act together, and Vicky and Laura got stuck into the treatments that have kept Laura alive. The good news is that the condition is now more widely known in the medical profession, and babies are routinely screened so that treatments can start early. Vicky worked hard to learn the nursing skills necessary to support her daughter, including giving injections, and she and Laura have also worked hard to live life to the full, fitting CF into their lives, not *vice versa*.

The event went down very well with the participants, many of whom were medical professionals and students who were not Members of The Society, and would not normally come to one of our events. A contingent of undergraduate physiotherapy students were particularly impressed with the relevance of physiological research to their future professional lives, and wondered if we might run more events on other health related topics. This has got us thinking of possibly staging events within medical and other health profession schools, something that would tally well with the objectives of our Working Group on Medical Training with the British Pharmacological Society. The success of the event means that we are planning to run it again in the near future at a venue likely to reach schools, media and the general public, at the BA Science Festival in September 2008.

Liz Bell

Systems biology and medicine: from reactive to predictive, personalised, preventative and participatory medicine

As our Society has a strong interest in systems biology, I went along to hear what Leroy Hood (President and co-founder, Institute for Systems Biology, Seattle, Washington), one of the entrepreneurs driving this, had to say when he gave the UK Focus for Biomedical Engineering Annual Lecture on 13 November . Hood is a very interesting character, his efforts in the area going back to his early work developing automated DNA sequencers and other instrumentation which enabled genomics to take off. He founded many new biotechnology companies on the back of these technologies, and realised in the 1980s that systems biology was going to be the way forward. He is convinced that a revolution is coming in medicine, with a move away from current reactive practices to a more personalised, predictive, patient centred medicine. This is only becoming possible from the development of a cross-disciplinary biology, where chemists, computing scientists, engineers, mathematicians and others are integral to the work. This was the ethos behind his setting up the Institute for Systems Biology in Washington. Engineers and biologists are both interested in doing parts assessments to analyse basic functions, and then to try to understand how the assemblage works when it is all connected up. Complexity is the challenge for 21st century biology, the one gene/one protein approach is limited. We are now seeing a grand convergence of genomics with modern computing making it possible to take a systems approach to the analysis of disease. Biology is an informational science with two basic types of information: the 'digital' core of the genome and the environmental information which modifies it. It is possible to look at our physiology as molecular machines executing individual functions, connected by biological networks that capture and transmit information. Disease arises from perturbations in these networks, eventually we should be able to design drugs to specifically re-engineer these.

So how could this change the world from the patient's and clinician's points of view? The hunt is on to find relevant diagnostic markers for various health and disease states in the blood. The aim is then to be able to do routine *in vitro* screening for patients using micro-fluidics/nanotechnologies, tying this into knowledge of a patient's personal genome, to generate probabilistic health histories. Clinical attention will shift towards a more preventative approach, focusing on promoting wellness rather than just treating disease. It is hoped that early, effective treatments and prevention will reverse the current escalating costs of medicine and make medical technologies more accessible to the developing world. The technologies involved will be 'disruptive'. IT, etc. will become essential in the training of physicians. How will medical schools adapt to this and the other changes that will be required? Hood's plans for the future include looking for a medical school willing to risk re-engineering itself to take these issues on board, and approaching Bill Gates to help set up a new Institute of Systems Biology to develop 3rd World capacity. He will be someone to watch with interest!

Liz Bell

Science and education

Always interested in what possible future Ministers think about things of concern to us, I went along to hear David Willetts, MP (Shadow Secretary of State for Innovation, Universities and Skills) give the Campaign for Science and Engineering Annual Lecture on 17 October. Somewhat predictably,

Leroy Hood, President and co-founder of the Institute for Systems Biology, Seattle.

Willetts praised science as being a central part of our culture, a fundamental value. In his view, schools had a natural dual role in training future scientists and in training others to appreciate science, and that our aim should be to make all children familiar with the scientific cast of mind. Maths teaching should be particularly supported in school, as this not only unlocks all the scientific disciplines but is also fundamental to understanding the economy. Scientific qualifications should be widely valued outside academia; people with science degrees who are not doing science jobs should not be regarded as failures as they are applying scientific modes of thinking to other essential problems. However, Willetts was concerned that science is in retreat in schools with many science and maths teachers not having appropriate qualifications, and only 58% of science specialist schools being able to offer separate biology, physics and chemistry courses. He thought that those teachers that are in place need the support of continuing professional development in science throughout their careers. School children need to understand that science degrees can have a life time premium of earnings of 40% above arts based subjects. The decline of practical science teaching was a particular loss, children need to experience the world in 3D, the 2D world of an increasingly screen based childhood does not develop this. I was left feeling rather unclear about what any future Government he might be a part of intended to do about any of this. We shall see!

Liz Bell

The role of the laboratory practical in undergraduate teaching

Maxine Lintern, right, questions the purpose of the extensive practical classes for physiology/science/medical undergraduates

This is a serious question as we can no longer take it for granted as an automatic part of the curriculum. Should practicals:

- demonstrate underlying principles/ concepts;
- re-enforce theoretical teaching received in lectures;
- build teamwork/communication and cooperative working skills;
- teach students how to generate useful data and develop their ability to interpret and understand it in light of a particular hypothesis;
- develop their understanding of research methods or 'how we do research';
- be fun...

Is it advisable, or even possible, to achieve these aims all of the time? Probably not. We have distinct groups of students working at different levels with different needs, not to mention variations in learning styles and approaches. We also have to consider the practicalities of lab teaching. It can be expensive, time consuming and hard work, especially with increased student numbers. However, we must still ensure there is a return on our 'investment' in terms of good learning for our students. How can we do this?

The first step may be to take a long hard look at our current provision and acknowledge that many practicals may end up as 'cookbooking' exercises. This is when students add A to B and, due to your well written lab script and the technical expertise of your staff, they more often than not get the intended C. They don't know (or even care) why they wanted C, or have anything more than a superficial idea of how they got it. If asked 'why did you add A to B?' they will answer something like, 'because is says so here in the script'. Effectively they are going through the motions without engaging with anything. What are they actually learning here? Possibly that experiments always work, and that you can get through them by 1630; not, I suspect, the intended take home message!

How can we get practicals to teach students what we want them to learn? Perhaps we need to use a range of practicals to focus on different things. For instance, if teaching how to measure and interpret an electrocardiogram, medical students need to learn this as a concept within a clinical framework for diagnosis and as a skill they will have to perfect to use on real patients. Science students, on the other hand, need to understand ECG within a scientific framework, to help them explore and question the latest research in cardiac function. Maybe it would help to separate out the 'skills learning' from the 'concepts learning'. This may help students to better understand what it is a practical session is trying to teach them. As students move to research labs for final year projects, 'skills' learning may need an additional boost. This can be done successfully as additional 'lab skills training' (Lintern, 2007), but could this skill acquisition be more explicit in all of the practical experiences?

Research skills such as enquiry, innovation and the ability to interpret are transferable attributes imperative for the employment destination of any science graduate. Are these then more important to most of our students than the underlying science principles? Before you throw your hands up in horror, I am not suggesting we take out the science, just that we may need to communicate more clearly the dual role of the practical class to our students. Otherwise there is a danger that they just become another part of the module landscape, and their impact as a unique learning opportunity is lost.

This leads to the question: what do our students think practicals are for, and is it the same as you?

Expectations

Do students learn from practicals (and other learning situations) what they think they should learn or what we tell them they should learn? It seems that students who expect to encounter concept/skill X in a practical will report that they have learned X, even if X is not actually part of the intended outcomes. Similarly, if they did not expect to learn Y, Y is not learned even if the lecturer thought it was an explicit outcome (Kirscher *et al*. 1993). Going back to our 'cookboooking' analogy this means that students who only see the practical as being A+B = C, will never consider the possibility, desirable or not, of getting D, E or F! Similarly, if they expect the practical (computer based, paper or wet) to be boring/pointless/not real learning/ just a game – it may well fulfil their expectations.

This behaviour is often influenced by previous experiences. When considering computer based learning (CBL), the conceptual gains made by students often depend on previous experiences with the www or other computer aided learning. Inexperience may encourage students to work through the package too quickly, see it as peripheral rather than central to the learning, and dismiss the concepts covered as trivial by association (Watson, 2001). Does this then mean that a student who has had a 'bad' experience now cannot learn from CBL, and does this extend to wet practicals too? There is some

evidence that students are often not sure what learning is supposed to look like. Phrases such as, 'independent learning' are misinterpreted as 'left to get on with it'. Differences between school and HE learning styles may mean that students have not been prepared for this kind of learning (Cooke & Hockings, 2007). Is this an even greater problem for lab based learning? If so, we may need a greater focus on support so that our students don't only go through the motions in our lab classes.

Perhaps we should be using new technologies even more to take advantage of the 24/7 anytime-anywhere approach to learning students now expect. The flexibility of virtual learning environments (VLEs) such as WebCT and Blackboard, and 're-usable learning objects' (RLOs) could give us a completely new way of teaching lab skills and concepts (not to mention more educational acronyms). Most importantly, they may give us the opportunity to encourage students to create their own learning experiences (James & Graham, 2007) which could engage students on a more personal level and consign 'cookbooking' to the past. These ideas are a long away from the 'lab class every Tuesday 1400–1700'!

Change of focus

How can we use the questions raised here to generate a way forward? Perhaps we need to primarily focus on what we want the lab class to achieve, i.e. the learning outcomes or objectives; and only then decide on how to achieve it. We then need to look very hard at the students' expectations for the practical and consider how we can develop these into what we want them to encounter and experience. In other words we need to interrogate the ability of the chosen method to deliver the learning outcomes from the student point of view. We may then need to train students to learn in this way. Effectively we must invest time in teaching students how to learn in practical classes, wet or dry.

This could involve separating out the various skills or 'jobs' that scientific research requires. For example, many practical classes are assessed by the lab report. Report writing is a skill in its own right which can be taught and assessed independently of experimental results generated in class. Another way of assessing 'results' may be via a 'journal of understanding' written by the students on what they think they have learned. This can be a better indicator of a student's progress, which cannot be 'cookbooked' and is hard to plagiarise. Similarly, if we want to explore how well a student can handle data, plot and interpret graphs, would a dry practical with given data do just as well as a learning tool? There is a danger that this approach will be perceived as 'pretend', but surely it is no more pretend than the completely structured lab class. By separating out the skills and concepts in this way we can ensure understanding and competence before putting them back together for more complex research projects. This kind of approach is not new and you probably use it in some areas, but the question is – do your students know and understand what you are doing?

We can take this further by actively and explicitly developing the students' ability to reflect on their own practice/learning styles/progress; possibly using their reflections for assessment (Nicol *et al*. 1994). This type of approach is much closer to the type of skills we need to see in our graduate research students. Put simply, the goal is to change the questions asked by students in laboratory classes from 'when will we finish?' to 'can I take another reading because I'm beginning to see a pattern …'

Interrogating your practice

This exploration of the role of the practical class in physiology teaching has posed many questions and not provided many answers. Only you can come up with these: for your students, in your practicals, in your environment. By interrogating our current practices in light of some of these issues and concerns we may be able to develop this exciting and fundamental teaching method to achieve all that we need it to, for the benefit of our students' learning experiences. Use the summary questions below as a tool to reflect on your lab classes and who knows where the answers may take you:

- what is the primary outcome of your practical class – skill, concept or both?
- how well does the practical integrate with the rest of the module?
- what are the student expectations/assumptions about the outcomes of the practical?
- how are you managing/developing these expectations to match your own?
- what is the best delivery method for the learning outcomes; wet, dry, virtual etc. in light of the student numbers, staff and resources?
- what is the students' experience of working with this method?
- do the students need help in learning to learn in this way?
- are students leaving the practical class understanding what it is they should have learned?
- is your practical class 'fit for purpose' and delivering the outcomes intended?

Maxine Lintern
Academic Practice and Organisational Development, University of Birmingham, UK

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A career scientist ... to be or what (else) to be?

I find myself in a position common among early career scientists. As I approach the end of my PhD I am facing the 'dilemma' about what to do next. Is an academic role for me? Or am I more suited to industry? Am I suited to being a scientist at all? Perhaps the big question is whether this really is a 'dilemma', or simply the most exciting opportunity a young scientist can ever have? This article aims to highlight some of the opportunities and choices available to young scientists as we aim to take our careers forward, and also to emphasise the excitement that can go with a career in research.

One major plus point of a scientific career is that science happens all over the world. Universities and industry have worldwide employment opportunities. Having the chance to spend time living and working in another country whilst actively pursuing a career is very attractive. Another plus is that the laboratory and analytical skills acquired during your PhD can be transferred from one area of research to another quite easily so if you get tired of your specific area of work there are sure to be opportunities to change to a new field using similar skills and expertise.

I have been lucky enough to spend time in both industry (as an undergraduate industrial placement student) and academia (as a technician and then a PhD student) and have my own opinions on the best bits of both. It is a personal choice and one doesn't beat the other – it depends on what you enjoy and where you like to apply your skills. In industry, exploratory research tends to be focused on specific diseases and involves working as part of a multidisciplinary team. Academic research can be much broader and often individual. Both can be rewarding and exciting but it is important to identify an area of work you are passionate about. Obviously, not everything is perfect.

Fiona Randall, our new Affiliate representative.

In science, there are the long hours in the laboratory and the constant pressures to get quality results and publications. The salaries can also seem disappointing when compared to careers in, for example, investment banking or finance. A graduate in those industries can often earn a similar or better salary to a post-doc in science.

At the International Brain Research Organisation conference in Melbourne, Australia (July 2007) I attended a symposium on epilepsy. At this symposium as well as leading scientists working in the field, they had invited patients with epilepsy to talk about their experiences with the disease. After a very emotional talk by a 20 year old girl who had been cured of very severe epilepsy by a temporal lobe resection, a PhD student in the audience stood up. He thanked the girl for her talk and said that, nearing the end of his PhD, he had started to become disillusioned about what to do next. She had reminded him of why he was doing research as scientific research does make a difference to people's lives. I felt inspired, as he had.

In my opinion the good points of what we do outweigh the bad; the constant learning and developing, the constant questions and challenges, the intellectual engagement and even the excitement when a good result comes out of a long day's experiment. There are job opportunities all over the world, conferences to attend worldwide, lots of intelligent and interesting people to meet and collaborate with and there are always more questions to answer. I can no longer imagine a future without these exciting challenges and I'm sure a lot of you feel the same.

Now I had better update my CV and start writing my thesis!

Fiona Randall
PhD Student in Neuroscience, Newcastle University, Newcastle upon Tyne, UK

Who are the true custodians of public opinions in science?

Rehana Jawadwala, our new special correspondent.

When we think about the role and responsibilities of a scientist, we think of rigorous research, answering questions about the natural world and investigating things that are as yet unknown. It is this inquisitiveness that is common to all those researchers who toil away in the dark hours. But how much thought do we give to our responsibilities to society? One such responsibility is communicating what we do. How often do we actually take pleasure in 'dumbing down' our complicated worlds? How often do we consider sharing our 'eureka' moments with

the public, the people who really matter, and (often) who ultimately pay our wages?

Scientists have a certain culture of being incomprehensible but, in my opinion, this elitist attitude will eventually slow us down.

I recently participated in the BA's Media Fellowship Scheme where, for a few weeks, I wore the hat of a science journalist. Yes, one of those very journalists we love to call names, those sly people who sensationalise science and who make all scientists look like mad boffins or meddlers with nature. I was as sceptical as they come; I had read stories about how the discovery of one gene was a panacea for curing disease, and headlines that claimed a 'super' pill that would cure cancers, obesity and everything in between. I often used to wonder how easy it was for journalists to pick up a complex scientific paper, interpret years of hard work, collaborations and theories and distil it into a 200 word piece; but I had no idea what was really involved until I actually had to do it myself.

And, to serve that sceptic in me right, I was placed with the *Daily Mirror*! I found myself going to press conferences given by scientific experts, explaining their studies in 20 min blocks. How could I, a scientist, not comprehend what they were saying? After all, I do very similar statistics and apply similar methods in my work. Slowly, as days went by, I realised where the glass wall lay. From where I sat this time around it was the scientists who found it difficult to make things simple and talk about their work as if it were an engaging story, leaving the poor journalists very little to hold on to. But when I sit at my desk in the lab, with my molecules dancing about in perfect harmony, performing a ballet, I see the lot – the story, the melody and the dance. And that is what the man on the street, the tax payer, wants to see as well. Surely we shouldn't deprive them of this performance – especially as it is ultimately their money we are all looking to tap into in our next funding bid. Furthermore, how can we ignore the same people who will benefit from the cures we search for?

So – I have now resolved that, if I can't write up my own work in a simple jargon-free 200 words, I will not go into the coffee room and talk about *The Sun* or the *Guardian* getting a story skewed. And I will not complain about the general public being complacent or ignorant when they voice their opinions on public health, scientific research methods and trends and education policies. As scientists, who tend to feel we 'own' this debate, we do not do our bit to educate them and keep them informed. And then, when the lobby groups get to them quicker, we only pucker up our noses in disgust.

So it is high time we all looked up from our spectrophotometers – or PCR machines or patch-clamp rigs – and participated whole- heartedly in getting our Society talking about science the way it should be talked about. In a nutshell – 'put up or shut up'. Or, best of all, **speak** up.

Rehana Jawadwala
Demonstrator/Researcher in Sports Science, Faculty of Science and Technology, University of Central Lancashire, Preston, UK

Celebrating 100 Years of Publishing Discovery in Physiology 1908-2008

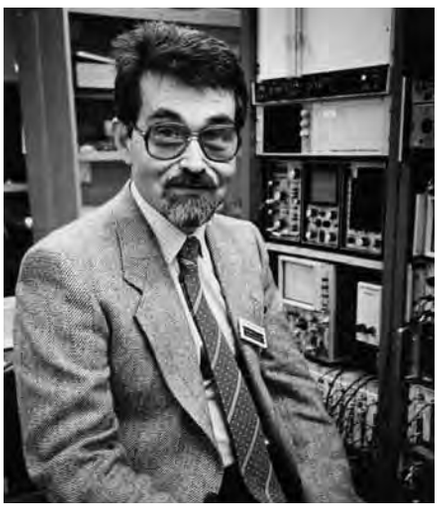
Experimental Physiology
Translation & Integration

Festschrift for K Michael Spyer

As part of Its Centenary celebrations *Experimental Physiology* is sponsoring a Festschrift in honour of K Michael Spyer, Professor of Physiology at University College, London, UK.

Friends and former colleagues including Jim Deuchars, Susan Deuchars, Brunello Ghelarducci, Michael Gilbey, Alexander Gourine, Robin McAllen, David Paterson, Julian Paton and Luis Silva-Carvalho will speak about their work with him.

The Festschrift will take place on Sunday 16 March from 1430 in the Centenary Gallery, Parkinson Building (right), University of Leeds, Those coming to Leeds for The Society's Themed Meeting *Determining Control of the cardiovascular system in health and disease: from brain to blood vessel* (17–19 March) are warmly invited to attend.



Michael Spyer in 1986 (left) and in 2007 (above) (*photos by Martin Rosenberg*).

In search of 'quality'

Quality is a word much bandied around in discussion about journals publishing, but what does it mean to those that produce and use a journal? An editorial in the latest issue of *Learned Publishing*, the journal of the Association of Learned and Professional Society Publishers, usefully dissects the concept into the aspects of the process that really matter to those involved.

For authors, a high-quality service means a fast but fair review, a simple-to-use submission system, helpful journal staff, accuracy in copy editing and typesetting, clear information about what is required of them during the publication process and how they may use the publisher-enhanced version of their paper, and efficient and wide dissemination of their work through publisher marketing and electronic means (linking and search engine indexing).

Editors look for quality in the support they receive for their unpaid services to a journal: an easy-to-use manuscript tracking system, the assistance of journal staff to relieve them of unnecessary admin. tasks, and, at the strategic editorial board level, sound advice on how they can contribute to the development of a journal.

Reviewers see quality in terms of the support system provided: a simple system for submitting reports and screening submissions to ensure their time is not wasted on inappropriate papers.

Readers need to have confidence that a journal will publish articles that describe current high-quality research. They want to be directed to the content of most interest to them and therefore appreciate filtering systems, both within a journal and on its publisher's web site, that allow them to focus quickly on relevant material. They want the articles they read to be concisely and clearly written and presented; like authors, they appreciate, often without recognising it, the services of expert copy-editors and typesetters.

Librarians bring financial considerations to the question of quality in publishing. They look primarily for value for money; the highest quality for the least cost. The impact factor of a journal, the recommendations of their institution's academic staff (who are also readers, authors, reviewers and editors), speed of publication, good 'findability' and usage of the content, and the cost determine the journals that make it onto their lists.

All these metrics of quality need careful management by editorial boards, journal staff and publisher partners. Economies of scale and automation can reduce costs without compromising quality, but people, those most expensive of commodities, are an essential part of the process. As Sally Morris says in her editorial: 'how well the links in the chain all communicate with each other are, in the end, a matter for the people who do them. All this costs time and money, but we economize on quality at our peril'.

Carol Huxley
Managing Editor, The Physiological Society Journals

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Symposia

The Journal of Physiology Symposia programme for 2008 will include:

Wednesday 9 April (0800–1000)
The role of GABA and glutamate on adult neurogenesis. At EB 2008, San Diego Convention Center, San Diego, CA, USA.

Saturday 26 April (1230–1635)
Retinal ganglion cells in model organisms: development, function and disease. An educational course co-sponsored by ARVO and The Physiological Society at Broward County Convention Center, Fort Lauderdale, FL, USA.

Thursday 10 to Saturday 12 July
Synaptic basis of disease. At FENS Forum of European Neuroscience, Centre Medical Universitaire, Geneva, Switzerland.

Full details and programmes at: http://jp.physoc.org

The Physiological Society EGM

17 March 2008

The Council of Trustees has resolved that an Extraordinary General Meeting be held on Monday 17 March in the Medical Lecture Theatre, Worsley Building (pictured below) at the University of Leeds at 1245.

The EGM takes place during The Society's Cardiac & Respiratory Themed Meeting. Each Ordinary and Honorary Member (including those registered as Retired) has the right to attend and vote at the EGM.

The business of the meeting will be to consider and, if thought fit, to pass two resolutions to amend the Articles of Association and Domestic Rules. These changes address the lines of authority within The Society, specifically within the Executive Committee, and clarify the system for the annual election of Council Members.

Normally such resolutions would be proposed at the AGM. However, with both the current President (Ole Petersen) and Chair of the Executive Committee (Ian McGrath) ending their terms of office in July 2008, the Council would like to implement the changes in time for the forthcoming elections for Council members and the Executive Committee.

If you will not be attending the EGM, the Council urges you to use your proxy vote to instruct the Chair of the EGM how you wish your vote to be cast. Proxy voting is online only, with a deadline of 14 March 2008.

For full information about the meeting and resolutions, and details of how to register a proxy vote see http://www.physoc.org/egm.

For further information, please contact Simon Kellas, Company Secretary, skellas@physoc.org or 020 7269 5725.

In brief ...

Congratulations to Society President Ole Petersen who was awarded a CBE for services to science in the New Year Honours List.

Society Member Ismaeel M Bin-Jaliah was elected Secretary General of the Saudi Society for Medical Educationin November 2007. Ismaeel is Assistant Professor of Neurophysiology and Director of the Medical Education Centre at King Khalid University in Abha, Aseer, Saudi Arabia.

The Paton Prize was established in 1994 by The Society's History and Archives Committee to encourage the study of the major ideas and concepts that have shaped modern physiology. The Prize takes the form of a bursary to support such studies, with funding of up to £1000 to cover travel and incidental expenses. The Committee wishes to promote interest in the history of physiology among younger Affiliates and Members of The Society, as well as established scientists. The bursaries are financed by the interest from the Paton Fund, an endowment originated by a donation from Professor Sir William Paton, with a matching donation from The Society. The first Paton Prize was awarded in 2007 to David Miller for his research into the life and work of Sydney Ringer (see p. 36). For more information on the Paton Prize, or to suggest a future recipient, please contact the Committee chairman, Dafydd Walters (dwalters@sgul.ac.uk).

The Editorial Board of *Experimental Physiology* is pleased to welcome five new Editors – Kenneth Baldwin (California, USA), Peying Fong (Kansas State, USA), Wayne Giles (Calgary, Canada), Stephen Harridge (London, UK) and David Murphy (Bristol, UK).

More details in the next issue.

BIOSCIENCES FEDERATION

Science skills in the 21st century

There are frequent reports and comments about the shortage of skills in the biosciences: shortages that are important and potentially damaging to the prosperity of our country. However 'skills' do not exist in some semi-independent context. It is always necessary to define what the 'skills' are needed for, and this can produce conflicts for those responsible for the delivery of our bioscience skill base.

The first skill that we all need is the skill to be a good and productive citizen. In a knowledge-driven economy, scientific skills should be part of the skills portfolio of as many citizens as possible, even though they do not themselves pursue a career in science. For me, it is highly desirable that we have more citizens who understand the scientific method, who appreciate the difference between probabilities and absolutes and who make decisions on the basis of evidence and not Luddite prejudice. With this training, public discussion about climate change, biodiversity or disease will be better informed and there will be greater understanding of the contribution that practicing scientists are making to the debate. In time, the public trust in scientists, which is already quite good, might improve further. The knowledge driven economy demands a scientifically literate population. Delivery of this essential skill is an important responsibility of our schools and universities.

However, more usually a skills shortage is used to describe a more specific problem than the generic need to have science as part of our everyday cultural base. The Biosciences Federation (BSF), together with the Association of the British Pharmaceutical Industry (ABPI), has just published a report entitled *In vivo sciences in the UK: sustaining the supply of skills in the 21st century* (the report is available at www.bsf.ac.uk). One of our recommendations is that a small number of Masters programmes could be introduced to help alleviate a shortage that is already with us and is having important effects in the pharma-ceutical sector. We propose 36 dedicated studentships for this programme for each of the next 3 years. This is an important area and yet the solution involves really small numbers: *in vivo* skills are definitely not required in all life science graduates. Of course, practical skills are very definitely required because most science and most biology are intensely practical subjects.

There are many other areas of the biosciences where skills are being lost and yet the solution needs relatively small numbers of practitioners. Take for example the field of systematics and taxonomy. There is no doubt that we are losing the capacity to identify precisely some of our native species – for example lichens. Yet we need really expert individuals in this area, today perhaps even more than in the past: we cannot monitor the effects of climate change on our flora and fauna unless we can identify species correctly! Perhaps we will end up relying on the 'gifted amateurs' who already contribute much in this area – but in this case the academic subject will be lost.

The production of modest numbers of high level experts in many areas of the biosciences is predominantly the responsibility of our universities and, to a lesser extent, the Research Councils. I write 'lesser extent' because some disciplines – for example taxonomy – can be internationally excellent without relying on large grants. And this leads to a second problem. Much biology today is rightly 'big science' – big grants and big teams. The business of running a university means that these big science teams are financially more attractive than those individuals virtually grant-free.

Furthermore, individuals without grants are likely to find it difficult to meet the charges that open access brings. The result, of course, is that there is real pressure on systematics and taxonomy (and many other minority skills) as a profession. However, the country needs these skills.

Clearly the skills landscape is complex and varied. The question to face is whether or not the delivery of highly specialised skills can continue to be left to the vagaries of the market place. This essay is not leading to a conclusion that, for example, all universities with a life science degree have Masters programmes for *in vivo* skills, or that all plant science departments have top level taxonomic skills. That would be absurd! But the question to answer is how we produce those experts that the country requires – and in sufficient numbers.

Not everyone will like the last sentence! Some will have a wider view, especially in the context of their own expertise! But that can be left to the market place. What we need is confidence that the UK will have the full portfolio of bioscience skills that will be essential if we are to maintain our strong global position in this area. These are skills that would be difficult to 'buy in' if our own skill base was lost.

What is needed is top down management, coupled with inducements, in order to build a few excellent teams in minority subjects that are nonetheless essential. Let funding be ring-fenced and universities/institutes compete for the money to provide leadership in these areas. This is not a new idea: it happens often. For example, if you want capital equipment for structural biology from the BBSRC you have to apply from one of about 10 universities. What is new is the argument that this should be done to sustain skills – and there is the key word. Any initiative must be sustainable in the long term. These are not arguments for 5 years and then the money can be recycled into some other project. These are arguments for a generation – and, sadly, as a consequence they will not seem very dynamic where it matters!

Richard Dyer
Chief Executive Officer

Jogging and global warming, or the Nike-Adidas CO_2 footprint

Have you ever wondered how much CO_2 all those frantic joggers add to the global warming problem? And how does it compare with travel by the vilified car? Given the result of some simple physiological calculations, I suspect some will be surprised.

A car running at about 40 mpg and 100 km per hour – very achievable for modern vehicles – will generate about 150g CO_2 per km (according to published data that you can check in any recent car advert). For an exercising, efficient human we can assume a near-maximum, steady-state, oxygen consumption of about 50ml O_2 per kg body weight per minute. Let's take the conventional 'textbook' 70kg man; that equates with 3.5 litres of O_2 consumed per minute. Assume, at this stage, that he's running his metabolism on carbohydrate; the respiratory quotient (RQ) for this substrate is about 1.0. This means his oxygen consumption will result in about 3.5 litres of CO_2 breathed out per minute. The density of CO_2 is nearly 2g per litre (under standard conditions) which means a CO_2 production of 7g per minute. He will also be running at close to his maximum, sustainable, aerobic speed. If our runner is pretty fit (... very fit!), he might be running at 5 minutes per mile rate, or approximately 3 minutes per kilometre. Thus, to run a kilometre, he will generate (3 x 7) = 21g of CO_2. Of course, if he was less fit or efficient, he'd be producing more CO_2 to cover each kilometre, and also taking longer over it.

So, if our car was carrying four people, over a 100 km trip it would generate some (150 x 100)/1000 = 15kg of CO_2. If those same four passengers were to ***run*** the 100 km instead of riding, they would generate about (4 x 21 x 100)/1000 = 8.4kg between them, a little over half as much as taking the car. But we have overlooked something. After about an hour, when the car arrives and stops, it ceases to produce any more CO_2. However, our passengers will still be respiring at their resting rate as will our runners too (once they have stopped puffing after their 100 km 'jog'). Thus, they carry on producing at least 30g of CO_2 per hour, day and night. Indeed they were still producing that much, even when being driven in the car. In 24 hours, after just one 100km trip, our four car travellers will generate 2.9kg themselves and their car 15kg; a total of just under 18kg for the day. The runners, who spent 5 hours running and 19 at rest, will produce (8.4 + (4 x 19 x 0.03)) = 10.7kg for the day. So, the car journey only produced an 'extra' CO_2 output comparable with four or five people sitting around doing nothing for a few days. If the journey were shorter, the CO_2 'gap' would obviously be less remarkable too. And furthermore, unlike the car, in order to run at this speed, our joggers would have to be jogging almost daily to keep fit between trips too; 'training' generates still more CO_2.

What's the alternative? If our travellers continued sitting around doing nothing, thereby becoming couch potatoes, they would not travel or run as far, but they would reduce their global CO_2 'footprint' by 75% for the day. But there is a further bonus. The term 'couch potato' is misleading because our idlers would lay down fat, not starch. Adipose tissue is surely an excellent way of sequestering carbon. The metabolic rate of adipose tissue, once built, is pretty close to zero. And when they do eventually come to burn it off, either in exercise or, I suppose, eventually in a crematorium, remember that the RQ for fat is only 0.7. Less CO_2 production in the end too!

More cynically still, has Gaia perhaps found the right strategy to save the planet by changing the shape and reducing the life expectancy of the average American (because they can't be persuaded out of their SUVs)? This is not for the squeamish – achieving ideal carbon sequestering requires an early death for our tubbies, ideally from an abrupt cause since wasting diseases rather defeat the objective (I said this was cynical). Obesity-driven CVS problems fit the remit. And finally, disposal of the body demands an hermetically-sealed mode of burial to avoid carbon recycling.

The arithmetic implies we should eat more and exercise less to help save the planet. I rather suspect a better answer lies elsewhere!

David Miller
Glasgow, UK

Tissue engineering

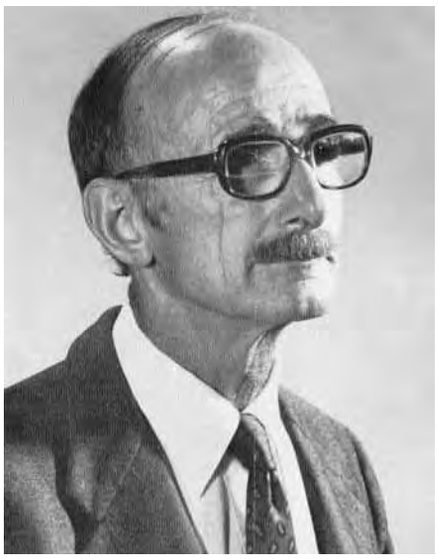
An NC3Rs/BBSRC free 1 day multi-disciplinary meeting on 30 April on *Engineering tissue alternatives to animals*, to highlight the potential of tissue engineering as a means of providing scientifically robust alternatives to animal models.

Information and registration (deadline 4 March) at: http://www.nc3rs.org.uk

Watch out for more exciting initiatives to come from the NC3Rs, now that Ian Pearson, Minister of State for Science and Innovation has announced that their funding is set to double over the next 3 years.

John Richard Pappenheimer

1915–2007



John Richard Pappenheimer, George Higginson Professor of Physiology, Emeritus, at Harvard Medical School died on 9 December at the age of 92.

John Pappenheimer's work in capillary permeability and molecular sieving are classics in physiological literature. He contributed valuable research to a wide range of disciplines within physiology: capillary permeability, respiratory physiology, blood-brain CSF transport, the neurochemical aspects of sleep, and most recently to the understanding of the absorption of sugars and amino acids in the intestine.

Born in NYC, Pappenheimer attended the Lincoln and Loomis schools. He received a BS from Harvard College and a PhD from Clare College, Cambridge, England. In 1953 he was awarded the lifetime Career Investigator position from the American Heart Association for his work on capillary permeability and in respiratory physiology. He was appointed the George Higginson Professor at Harvard Medical School in 1969. He was a member of the American Physiological Society (President 1964-1965), the Academy of Arts and Sciences, the National Academy of Sciences and Honorary Member of The Physiological Society. He published numerous articles of original work over a span of 70 years. He collaborated with colleagues from around the world, including Frank Winton, Glen Millikan, Bjorn Folkow, Manfred Karnofsky, JM Krueger, J Madara and Charles Michel.

An avid mountain climber, skier, gardener, tennis player, woodsman, and `cellist, John Pappenheimer embodied the Renaissance man. In 1949 he married the violinist Helena F Palmer, with whom he shared a passion for quartets. Together they raised four children, three golden retrievers and numerous goats. He leaves behind his wife of 58 years, Helena Palmer, Cambridge MA, three children (Will Pappenheimer, NYC/Tyringham MA, Rosamond Zimmermann, Lexington MA and Rick Plant, Melbourne, Australia), five grand children (Leo and Martha Zimmermann, Rudy Ott, Ramsay and Freya Plant).

Rosamond Zimmermann

Charles Michel writes:
John Pappenheimer was unique among 20th century physiologists in the wide range of topics that he influenced, attacking different questions with imaginatively designed experiments and bold reasoning. During his period as a research student of Frank Winton in 1930s' Cambridge he learnt the methods of classical mammalian physiology and he went on to combine these skills with a rigorous quantitative approach and remarkable grasp of physical principles. These qualities are most conspicuous in his two classic papers on capillary permeability in 1948 and 1951. The first reveals a close attention to experimental detail and describes highly reproducible results leading to clear conclusions. The much longer 1951 paper uses the same experimental methods in an imaginative experimental design to make the first estimates of microvascular permeability and then develops a new theory of restricted diffusion through membrane pores to interpret the data. The latter is itself a *tour de force*.

This work on microvascular permeability was carried out with two visiting post-doctoral fellows (Soto-Rivera and Borrero) and a research student (EM Renkin) when John Pappenheimer was in his mid 30s. By the time he was 40, his other investigations had had a major impact on studies of muscle blood flow, haemodynamics, on measurements of respiratory dead space and on the autoregulation of renal blood flow. In addition, he had published papers with Winton on the effects of diuretics in the isolated perfused kidney and spent the period 1940–1945 monitoring hypoxia in USAF pilots and developing onboard oxygen generators for aircrew. In the second half of his life he would go on to make the first quantitative measurements of CSF secretion and drainage in conscious animals, make major contributions to the central chemical control of breathing, pioneer the investigation of the neurochemical basis of sleep and then – after retiring when he was well into his 70s – publish three sequential papers In the *Journal of Membrane Biology* on intestinal absorption. In all these investigations he carried out experiments himself and sometimes with a research student or a post-doctoral fellow. He continued to work on intestinal absorption seeing his last full paper published in *The Journal of Physiology* when he was 88.

Some of his conclusions led to controversy and his theory for the autoregulation of renal blood flow was shown to be incorrect. He had no regrets about this, pointing out that at the time he put forward his 'plasma skimming' theory, it was clearer than any other idea of autoregulation, and that it had provoked others to carry out experiments to disprove it.

This attitude is stated at the end of his Bayliss-Starling lecture (on sleep) at UCL in 1982, when he quoted Bayliss '... it is better to hold to a well-understood and intelligent opinion even when it is wrong, than to be content with a (muddle-headed) mixture of conflicting views …'

From his experiences as a research student, John Pappenheimer retained a deep affection for this country and particularly for Cambridge and for The Physiological Society. He greatly valued his Honorary membership of The Society and took a continuing interest in The Society's development. Apart from numerous brief visits and the occasional holiday in the UK he spent the academic year 1971/72 as a visiting fellow at Churchill College Cambridge and 1975/76 as George Eastmann Visiting Professor at Oxford. An internationalist, he was critical of the inward looking attitudes of some of his American colleagues and devoted much time to the IUPS, serving for 9 years on its Council.

I first met him nearly 40 years ago and, while initially being in awe of his legendary reputation, was delighted by his friendliness and encouragement, particularly as I soon saw how devastatingly critical he could be in discussions at scientific meetings. As I came to know him informally, casual conversations revealed his astonishing breadth of knowledge of English and American literature, of world history and current affairs, quite apart from music, which was probably equal to science in his priorities. It was immensely stimulating to talk to him and even when he was in his late 80s he was full of challenging questions and gentle humour. It was a great privilege to have known him and worked with him for undoubtedly he was one of the greatest physiologists of the 20th century and a very remarkable and delightful person.

The Society also notes with regret the deaths of Margaret Stanier and Peter Lewis.

Margaret became a Society Member in 1964. Based at Babraham, she was a Fellow of Newnham College, Cambridge where she was well known to many medical students.

Peter, a pioneer in the cholinesterase field, became a Member in 1954.

John Ramsey Bronk

1929–2007

Ramsey Bronk, first Professor of Biochemistry at the University of York, died at the age of 78 in Oxford.

Ramsey grew up in Pennsylvania and was exposed to the company of scientists at an early age. His father, Detlev Bronk, was President of the then Rockefeller Institute (now Rockefeller University) and later of the US National Academy of Sciences. After graduation from Princeton University, Ramsey came as a Rhodes Scholar to Oxford in 1952. There he studied for his doctoral degree in the laboratory of the great intestinal physiologists Fisher and Parsons, where he met his wife Sylvia. They returned to Washington in 1956, where they both worked in the National Institutes of Health. Two years later, Ramsey was appointed as Associate Professor of Zoology at Columbia University, where he became full Professor shortly before coming to York. Ramsey was appointed as Professor of Biochemistry by York's first Vice-Chancellor, Lord James, to the Department of Biology headed by Mark Williamson; Ramsey arrived in October 1966 and remained until his retirement in 1997.

Ramsey was instrumental in setting up and developing the very successful biochemistry degree course run jointly by the Departments of Biology and Chemistry. He oversaw the provision of equipment needs essential to the successful launch of biochemistry teaching and research at the University. Many staff had cause to be grateful to Ramsey for he was very supportive of staff at all levels. In particular, Ramsey took a special interest in the technical staff and matters affecting their welfare and career development long before the more formal systems of today. He also played a key role in setting up cancer research in the Biology Department with laboratories funded by Yorkshire Cancer Research.

Ramsey had a deep understanding of metabolism, which formed a large part of his teaching. He wrote two major successful textbooks; one, *Chemical biology*, which reflected the nature of the York degree course, and the other, *Human metabolism*, which I subsequently used as a textbook for the course we had taught in together. His tutorials, in particular, were very much appreciated by the students. In research, Ramsey was one of the first to appreciate the importance of mitochondria and he produced ground-breaking papers on the regulation of oxidative phosphorylation by thyroid hormones. Subsequently he worked extensively on metabolic aspects of chemotherapeutic drug delivery by peptide transport across the small intestine. His long-standing collaboration with Richard Boyd (Oxford) and Pat Bailey (Keele) contributed strong evidence for the now accepted view that peptide transport is proton-dependent, as opposed to the sodium-dependent transport of many other nutrients. Their work also contributed much to the structural understanding of the delivery of peptide-linked drugs. Always happy to suggest new ideas, Ramsey transformed me in mid-career from a structural biologist to an intestinal physiologist simply by asking me, in the course of one of our many chats, if I would supervise a final year undergraduate project on intestine.

Brought up in America, but a lover of all things English, Ramsey became essentially a mid-Atlantic figure and was also a strong supporter of European Science. He was a founding member of, and regular contributor to, the European Intestinal Transport Group and Chairman of the European Editorial Committee of *Physiological Reviews*, as well as a Distributing Editor for *The Journal of Physiology*.

Ramsey was an expert yachtsman, an accomplished carpenter and an able cook. A great family man, he leaves behind his wife of 52 years, Sylvia, their sons, Richard and Christopher, who are both in academic life, and four grandchildren, Justin, Philip, Edmund and Eleanor.

George Kellett

Regulatory mechanisms of striated muscle contraction

Volume 592, Advances in experimental medicine and biology. Edited by S Ebashi & I Ohtsuki. Springer,Tokyo, Berlin, Heidelberg and New York. 407 pp, UK price £96.00
ISBN 10-4-431-38451-0

A *Festschrift* for a great scientist tends either to be largely historical or to be a state of the art survey of the field that the master initiated. It is rare that it manages to be both. Volume 592 of *Advances in experimental medicine and biology* is the proceedings of a meeting held at Okazaki, Japan in 2005 to commemorate the 40th anniversary of the discovery of the filament-based troponin-tropomyosin regulatory system by Setsuro Ebashi (Ebashi, 1963; Ebashi *et al*. 1964; Ebashi *et al*. 1969).

This volume does indeed address both aspects of the *Festschrift* and does so remarkably well. The list of attendees was outstanding and studded with luminaries; Ebashi himself, both Andrew and Hugh Huxley, John Gergely, Andrew Szent-Györgyi and Makato Endo (most of them in their ninth decade). The younger cohort featured Mike Geeves, Yuchiro Maeda, Rick Moss and John Solaro, among many others. Warm messages were received from Sam Perry and Annemarie Weber, who were both too infirm to travel so far. Only Jean Hanson, who died tragically early in 1973, was absent from the roll-call. Like the D-day veterans reviewed by Queen Elizabeth on the beaches at Arromanches in 2004, we shall probably not see such a parade again.

Ebashi was among the most important post-WWII Japanese muscle scientists and was very well known outside his native land. He was a Foreign Member of the Royal Society and in 1979 gave a memorable Croonian Lecture on *The regulation of muscle contraction* (Ebashi, 1979). That lecture lucidly reviewed the history of the recognition of the calcium ion as the sole regulatory factor of muscle contraction at the molecular level and the role of the troponin-tropomyosin system in responding to changes in the calcium levels. It bears mentioning that this story was initially controversial. Annemarie Weber in her letter in the Volume reminds us that, at the Dedham muscle conference in 1962, she and Ebashi were in a distinct minority who then accepted the role of the calcium ion as a messenger. It was the persistence and the careful experiments of that minority that finally gave the scientific community the picture that now graces all the text books. The history of this work, set out in several papers in the first part of this book, deserves a very careful read and holds lessons for us all. Sam Perry's letter emphasised that some details of the picture are still controversial, perhaps the mark of an active scientific field.

The other major part of this book is made up of many useful accounts of the current state of research by the protagonists of today. Any selection is bound to be a personal matter – I was particularly interested in Mike Geeves' chapter, which sets out clearly the difference between the Ca^{2+}- dependent behaviour of the extracted proteins and that of the muscle myofibril *in situ*. Yuchiro Maeda's papers on the crystallography of the troponin complex were also impressive. Finally, as the husband of someone working in a Department of Cardiovascular Medicine I will find Section III (*Regulation in cardiac muscle and disorders*) of great value.

This book should certainly be on the shelves of all research workers and research groups in the field, as a source of both inspiration and reference. Iwao Ohtsuki, the co-editor, remarks in the introduction that Ebashi and he had hoped that the book would '*become a milestone for future developments in the study of the regulation of muscle contraction and related biomedical sciences*'. I hope they are successful in that objective, as the book deserves it. Unfortunately, though, the price will be prohibitive for any young research worker. Can scientific publishers do nothing to deal with this problem? I see that when I purchased the proceedings of the 1962 Dedham conference it cost me US $18.00, about £60 in today's money. The difference between £60 and £96 may seem little enough, but junior researcher's or lecturer's salaries are not now what they were then, and surely desk-top publishing should have slashed production costs in the intervening 45 years?

Setsuro Ebashi himself was already disabled from the residual effects of a stroke in 2000 when the *Festschrift* meeting took place; he attended some sessions in a wheel-chair, loyally and lovingly supported by Fumiko Ebashi, his wife and long-term scientific collaborator. A video record was made for him to follow at his leisure. Very sadly he died in July 2006 before the final publication of this volume (Editor-in-Chief, 2007). The Japanese meeting and this book can stand, though, as a fitting tribute to a humane man and a very great scientist.

Gerald Elliott

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Neurobiology of Alzheimer's disease
Molecular and cellular neurobiology, 3rd Edition

Edited by David Dawbarn & Shelley J Allen. 2007, Oxford University Press, Oxford.
468 pp, £49.95
ISBN 0-19-856661-1

It is estimated that 18–24 million people suffer from Alzheimer's disease (AD) worldwide. AD is marked by dementia. At autopsy, extracellular amyloid plaques, containing amyloid Aβ, and intracellular neurofibrillary tangles containing the tau protein, which normally stabilises microtubules, are found in the neocortex and hippocampus, which become progressively atrophied. Early diagnosis is important and it is imperative that new biochemical markers and imaging techniques should be found to aid diagnosis, with a hope that future research will lead to therapies that slow or halt the progress of AD.

This book sets out to give 'an accessible overview of the major areas of knowledge and controversy' in research on AD. Within the confines of a multi-author volume, it does it very well in a fast moving area in which the editors claim that nearly half of the papers have been published since 2000. The chapters are well chosen and well written by an international team of contributors, with good use of headings to guide readers through the text. Each chapter has a substantial bibliography. My major criticism is that the volume would have been better divided into sections, and that the chapter sequence could have been improved.

The book starts with a review of 100 years of investigation into AD and is followed by chapters on neuropathology, genetics, molecular biology and biochemistry, including a chapter on protein misfolding, aggregation and fibril formation. Various model systems are then discussed as is the role of anti-inflammatory drugs to delay onset and slow disease progression. The cellular targets of amyloid β peptide are considered and two later chapters consider amyloid-based therapies for diagnosis, prevention or treatment of AD. Intervening chapters deal with neuro-transmitters, nerve growth factors, clinical assessment of AD, molecular and biological markers and current pharmacological approaches to treatment – the ordering of the chapters could have been better.

All things considered, if you want to know more of what is going on in terms of understanding and treating Alzheimer's disease, then this book is for you, but remember that what you are seeing is a snapshot of what was happening up to 2006. I look forward to future editions to see what further advances have been achieved in our understanding of this deeply distressing, progressive illness.

Bill Winlow

Insulin murders: true life cases

By Vincent Marks & Caroline Richmond
RSM Press, 2007. 190 pp, £12.95
ISBN 978-1-85315-760-8

Like any strong medicine, insulin can be used for good or ill. The miracle drug which transformed the outlook for the previously rapidly fatal disease of diabetes was first recorded in a case of attempted suicide as early as 1927. But the first case of murder proved to have been caused by insulin was not until 1957, in England. Since then, Vincent Marks, a clinical biochemist with a special interest in hypoglycaemia, has collected about 50 other instances. Reports of 14 well documented cases, often involving Marks in the expert witness stand, make up this book. The style is somewhat quirky, but easy to read, thanks to the efforts of Caroline Richmond, a medical journalist who has collaborated on the project.

In reality there are two stories here. The first is the14 cases themselves, which raise some interesting issues regarding the actions of insulin which are not well known to either clinicians or scientists. For example, there are several cases in which substantial significance is placed on the observation that vomiting is very rare in severe hypoglycaemia induced by insulin, though it does occur in hypoglycaemia due to other causes, such as sepsis. The explanation offered is that insulin-induced hypoglycaemia speeds the transit of food from the stomach to the small intestine, and that this is an adaptive mechanism to expedite the passage of glucose back into the bloodstream. Interesting idea, but it may be that there's more work to be done here. Since sepsis-induced hypoglycaemia does cause vomiting (and presumably also responsive hypoinsulinaemia), this seems to imply that there are more wrinkles to the story of glucose, insulin and gastic emptying than are immediately apparent. Is it the interplay of these factors that inhibits vomiting in insulin overdose, or is it a specific effect of very high or very low insulin levels, or something else entirely?

The book's other story (though one that is told indirectly and would have benfited from a chapter of its own) is that of the methods used to measure insulin. In the past these have been fraught with unreliability and caveats of the sort that courts neither understand, nor seem to take much interest in, preferring to hope that an expert witness will clear it all up for them. The thing that will probably surprise and alarm you, is that although the tests have improved, it remains true to this day that the results of forensic biochemistry are not at all straightforward to interpret, even for something as apparently clearcut as insulin. Expert witnesses often disagree on the meaning of forensic results, and the

courts often fail to follow the arguments and try to latch on to "the truth" of scientific certainty, when they should instead be trying to understand forensic results in their correct statistical and case-based context as one piece of evidence among many. There is at least one case in the book which seems a clear miscarriage of justice, with an individual serving a long prison sentence for a crime that almost certainly never existed. Worryingly, the appeal court seemed no clearer in its understanding of the scientific evidence than the original judge had been. Here too there are many issues which need more work both at the bench and in the courts.

I recommend Insulin Murders as an interesting general read, but also as food for thought for those with a scientific interest in insulin and hypoglycaemia, since it seems to me that the book raises more questions than it answers.

John A Lee

Neuro-ophthalmology: neuronal control of eye movements

Edited by A Straube & U Büttner. 2007, Karger. 198 pp, €141.50
ISBN 978-3-8055-8251-3

If the eyes are the windows on the soul, then the small group of oculomotor neurones are what ensures that they are deployed to maximum effect. But any idea that analysis of the co-operative movements of the six pairs of eye muscles involved might be relatively simple was quickly dispelled a long time ago. As befits such important portals, there's a lot more to it than up and down, left and right. Hardly any of the muscles insert into a straightforward position on the globe of the eye with respect to its axis, there's torsion to consider (torsion?), and, given how sensitive the eyes are and how quickly they flit about, how do you measure what's going on anyway? It's a tribute to the perseverance of physiologists that the answers now amount to some pretty meaty tomes.

Out of this work have emerged many general principles, such as 'All extraocular motorneurones are involved in all eye movements and innervate basically functionally similar muscles.' Well that's what I thought too. But it is the purpose of this slim but excellent update volume, an emanation almost entirely from German departments led by Munich, to refine our ideas on this and many other matters. In fact, it turns out that distinct twitch and non-twitch motor fibres are present within the eye muscles and are differentially distributed, that they are innervated by distinct populations of neurones with their own positions in the oculomotor nuclei, and that these neurones receive different inputs from premotor locations in the brainstem. Excellent, more complications. But very interesting too. In addition to a chapter detailing these new anatomical niceties, there are contributions on methods of recording eye movements, the mechanics of the orbit and contributions of the eyelid, saccadic, smooth pursuit and disconjugate eye movements, optokinetic nystagmus, and the vestibulo-ocular reflex. In addition, there is a modelling chapter, and one considering the therapuetic considerations for eye movement disorders emerging from new findings. I first became interested in the oculomotor system as a student when I read the chapter on it in my copy of the 14th (and sadly the last) edition of Mountcastle's superb physiology text, and it continues to amaze me how much new and insightful and fascinating and relevant work is still being done on this rather small (though admittedly very important) group of nerves and muscles. This really very good and highly recommended update volume shows that the march of new ideas in this field shows no sign of abating.

John A Lee

Essays in biochemistry – oxygen sensing and hypoxia-induced responses

Edited by Chris Peers. Portland Press, Colchester, 2007.
184 pp, £21.95
ISBN 1-85578-160-3

Oxygen is essential for most forms of life. Though hypoxia does not normally occur under physiological conditions, there are a number of pathological states where it does. This publication is an overview of current research on oxygen sensing, responses instigated by hypoxia and pathological states linked with hypoxia. Each chapter is well laid out with an abstract, introduction, conclusion and summary; the cited references are an invaluable source of further reading.

Coleman and Ratcliffe introduce HIF (Hypoxia Inducible Factor) and its modification, Bell and Chandel highlight the role of mitochondrial reactive oxygen species in its activation by hypoxia, providing a good introduction to HIF. Galkin, Higgs and Moncada examine the multiple roles of nitric oxide in response to hypoxia.

Kumar and Evans discuss oxygen sensing in specialised tissues in chapters on the carotid body and pulmonary vasculature respectively. Kemp and Peers focus on ion channels that respond to hypoxia; these three chapters also discuss chemotransduction mechanisms in hypoxia sensing. Hue and Rider review AMP-activated protein kinase, an enzyme cited in earlier chapters as a putative hypoxia sensor.

Nanduri and Prabhakar discuss the clinical significance of intermittent hypoxia, while Paffett and Walker follow on by outlining the vascular adaptations resulting from chronic hypoxia. LaManna takes a look at how the brain to adapts in chronic hypoxia.

The last two sections deal with hypoxia and pathological conditions - Peers, Pearson and Boyles linking hypoxia to Alzheimer's disease, Brahimi-Horn and Pouyssegur looking at hypoxia and HIF in tumour development.

There is overlap between some of the chapters, inevitable when sections are written by different authors. The text forms a good introduction to those at degree level and those new to hypoxia, though it is also a good resource for those more familiar with the field.

Selina Pearson

Other books recently received

Observed brain dynamics by Partha Mitra and Hemant Bokil.

Sex differences in the brain: from genes to behavior. Edited by Jill B Becker, Karen J Berkley, Nori Geary, Elizabeth Hampson, James P Herman and Elizabeth Young.

Meetings (http://www.physoc.org/meetings)

2008

Leeds, UK (17–19 March)
Cardiac & Respiratory Physiology Themed Meeting with a Focused Symposium on *Determining control of the cardiovascular system in health and disease: from brain to blood vessel*.

Cambridge, UK (14–16 July)
Main Annual Meeting.

Oxford, UK (9–11 September)
Metabolism & Endocrinology Themed Meeting with a Focused Symposium on *Orchestration of metabolism in health and disease*.

Shanghai, China (12–16 September)
International Workshop on *Latest advances in ion channel techniques applied to physiological problems*.

Beijing, China (20–22 October)
Joint International Meeting of The Physiological Society with the Chinese Association for Physiological Sciences and the Canadian, Australian and American Physiological Societies.

King's College London, UK (15–17 December)
Vascular & Smooth Muscle Physiology Themed Meeting with a Focused Symposium on *Vascular responses to mechanical stress: cellular cross-talk and integration*.

2009

University College Dublin, Republic of Ireland (6–10 July)
Main Annual Meeting.

Woods Hole, MA, USA (September)
Joint International Meeting of The Physiological Society with the Society of General Physiologists on *Basic biology and disease of muscle*.

A collection of firsts

On the time taken in transmission of reflex impulses in the spinal cord of the frog
Florence Buchanan (1908). *Q J Exp Physiol* **1**, 1–66.

In January 1908, the *Quarterly Journal of Experimental Physiology* (now simply *Experimental Physiology*) published its first ever issue. The first paper in this historic first volume is also a first in another way, since its single author is Florence Buchanan, one of the first group of five women elected to The Physiological Society in 1915. Florence Buchanan worked for many years in Oxford, first with John Burdon-Sanderson, though she published her papers independently (they do appear together as authors on several communications to The Society). After Burdon-Sanderson's death Buchanan continued working alone.

The paper, at a heroic 66 pages, concerns the speed of spinal cord neurone excitation of skeletal muscle reflexes. The preparation is not very different from the classic frog sciatic nerve-gastrocnemius muscle, with nerve stimulation and EMG recording from the muscle surface. The figures look a little unfamiliar to a modern eye, since they show tracings recorded with a capillary electrometer which have to be read 'backwards', from right to left.

Despite her undoubted status as a pioneering British woman physiologist, relatively little is known about Florence Buchanan, as Tilli Tansey has previously commented (Tansey, 1993). Buchanan was born in Marylebone in London in 1868, the daughter of the physician, epidemiologist and civil servant George Buchanan (1831–1895), later Sir George Buchanan FRS and a long-time friend of Burdon-Sanderson. Buchanan was a pioneer of public health medicine in Victorian Britain, ultimately becoming Chief Medical Officer, and a medical contemporary of Burdon Sanderson's in the latter's pre-physiology career as a physician. Both men served as 'Medical Officers of Health' – public health doctors – for inner London districts in the 1850s and 60s, Buchanan for St Giles and Burdon-Sanderson for Paddington. It thus seems highly likely that Burdon-Sanderson knew Florence Buchanan from the time she was born. Buchanan attended University College London in the late 1880s, where she was taught and influenced by the eminent (and socially progressive) comparative anatomist E Ray Lankester. Her first published papers, on invertebrate anatomy, appear between 1889 and 1893 in the *Quarterly Journal of Microscopical Science*, forerunner of the present-day *Journal of Cell Science.*

Precisely when Buchanan began working with Burdon-Sanderson in Oxford is unknown, although it seems likely to have been the mid 1890s. In June 1896 in Oxford Buchanan achieved another landmark as the first woman to be present – as a guest – at a Society meeting. In her first paper from Oxford, published in 1899 in *The Journal of Physiology,* she states that the experiments 'were begun in October 1896'.

Oxford at the end of the 19th century was rather unwelcoming to women, who were not considered suitable or probably even eligible for College Fellowships. In addition, the Oxford of the 1880s and 90s was dominated by the attitudes of the Anglican Church, and notably less receptive to science in general than either Cambridge or UCL. After Burdon-Sanderson arrived to occupy the new Waynflete Chair in Physiology in 1882 he had to battle anti-vivisectionists within the University to get a lab built at all, though he won through, overseeing the opening of the Physiological Laboratory and becoming Regius Professor of Medicine in 1895. Burdon-Sanderson retired in 1904 and died in November 1905, just over 2 years before the publication of Buchanan's *Q J Exp Physiol* paper. The paper contains the following extended acknowledgement to him:

'*All the experiments described ... were made with apparatus which belonged to Sir John Burdon-Sanderson, and on which he had spent a great deal of labour, time, and money ... I had already been using it in its different stages for some years, and any work that has yet been done or will be done with it may in a sense be regarded as a continuation of his work. That this should be continued, and that what was already done in his lifetime should be made use of to the fullest extent possible for suggesting new lines of research and for the acquirement of new knowledge, is, I feel sure, the tribute to his memory which he himself would most desire*'.

Buchanan also thanks Professor (Charles) Sherrington, then in Liverpool but later to occupy the Waynflete Chair in Oxford '*for valuable criticism and for the interest he has taken in the work*'. Coincidentally, the second paper in this first volume of *Q J Exp Physiol* is by Sherrington.

Buchanan's earlier *J Physiol* papers of 1899 and 1901– the latter a monumental 77 pages – are '*from the Physiological Laboratory*', but later in her time at Oxford she held a post in the University Museum – where institutional hostility to women was less than in the Colleges – and this is the affiliation listed on the 1908 paper. Buchanan was clearly a figure of some note in early 20th century physiology, receiving grant support from the Royal Society – acknowledged in the paper – and presenting work to them. She had earlier gained a DSc from the University of London in 1902. Her last paper on spinal reflexes appeared in 1912, also in *Q J Exp Physiol*, but even before this she had started to work on investigating cardiac electrical events via ECG recordings. She later published several papers on heart rate in different animals and birds. In September 1913 Buchanan is listed as a speaker at the 9th International Congress of Physiological Sciences (now IUPS) in Groningen on *Cardiac events observed with the ECG*.

Shortly after this Buchanan finally achieved membership of The Physiological Society, nearly 20 years after she had first attended a Society scientific meeting, and more than 15 years after her first *J Physiol* paper. Had she been a man, it seems inconceivable Buchanan would not have been elected a Member in the 1890s. However, women were not then eligible and she had to wait until her middle age. The story of the debate over admitting women to The Society is entertainingly recounted by Tansey (1993).

Buchanan's career is harder to trace after her last publication in *Q J Exp Physiol* in 1912 and the Groningen Conference the following year, though she is later mentioned as 'retiring from [a job as] a part time lecturer' at Royal Holloway College in 1921. It seems likely that she died in the mid 1930s, since a bequest to the Marine Biological Association (MBA) in her name is listed in the MBA records for 1936–8.

Austin Elliott

Reference

Tansey T (1993). In *Women Physiologists*, Chapter 1, ed Bindman L, Brading A & Tansey T. Portland Press, London & Chapel Hill.

Themed Meeting

Theme
Cardiac & Respiratory Physiology

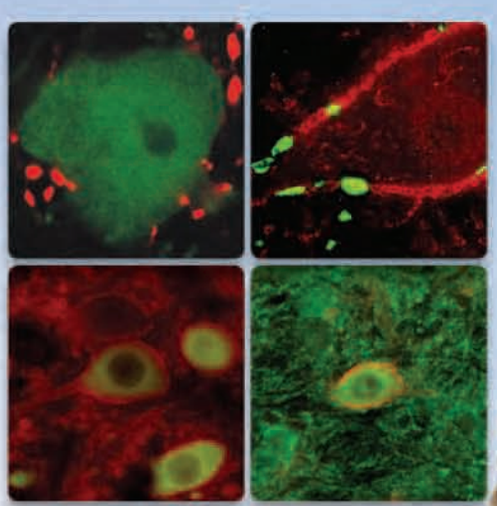
The Physiological Society

Determining control of the cardiovascular system in health and disease: from brain to blood vessel

University of Leeds, UK, 17–19 March 2008

Abstract submission and registration	Abstract submission	Early-bird registration	Registration
Opens 14 January 2008	Closes 31 January 2008	Closes 22 February 2008	Closes 10 March 2008

The Physiological Society travel grant deadline is 31 January 2008



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Organisers: Jim Deuchars and Sue Deuchars (University of Leeds, UK)

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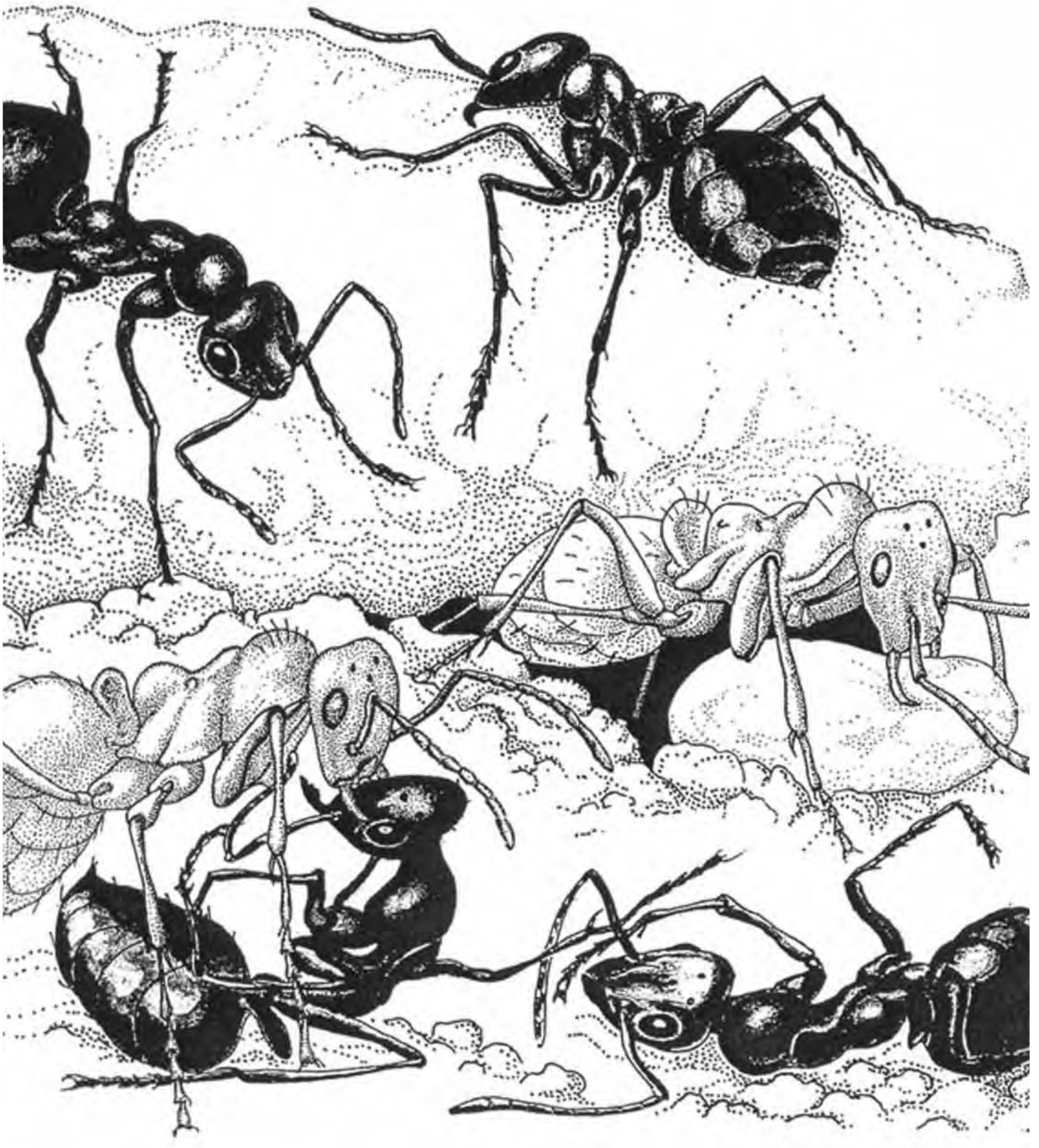

Amazon ants (*Polyergus rufescens*, light colour) raiding a colony of *Formica fusca* (dark colour), whose nest is in dry soil under a stone (Living History, p. 10)

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