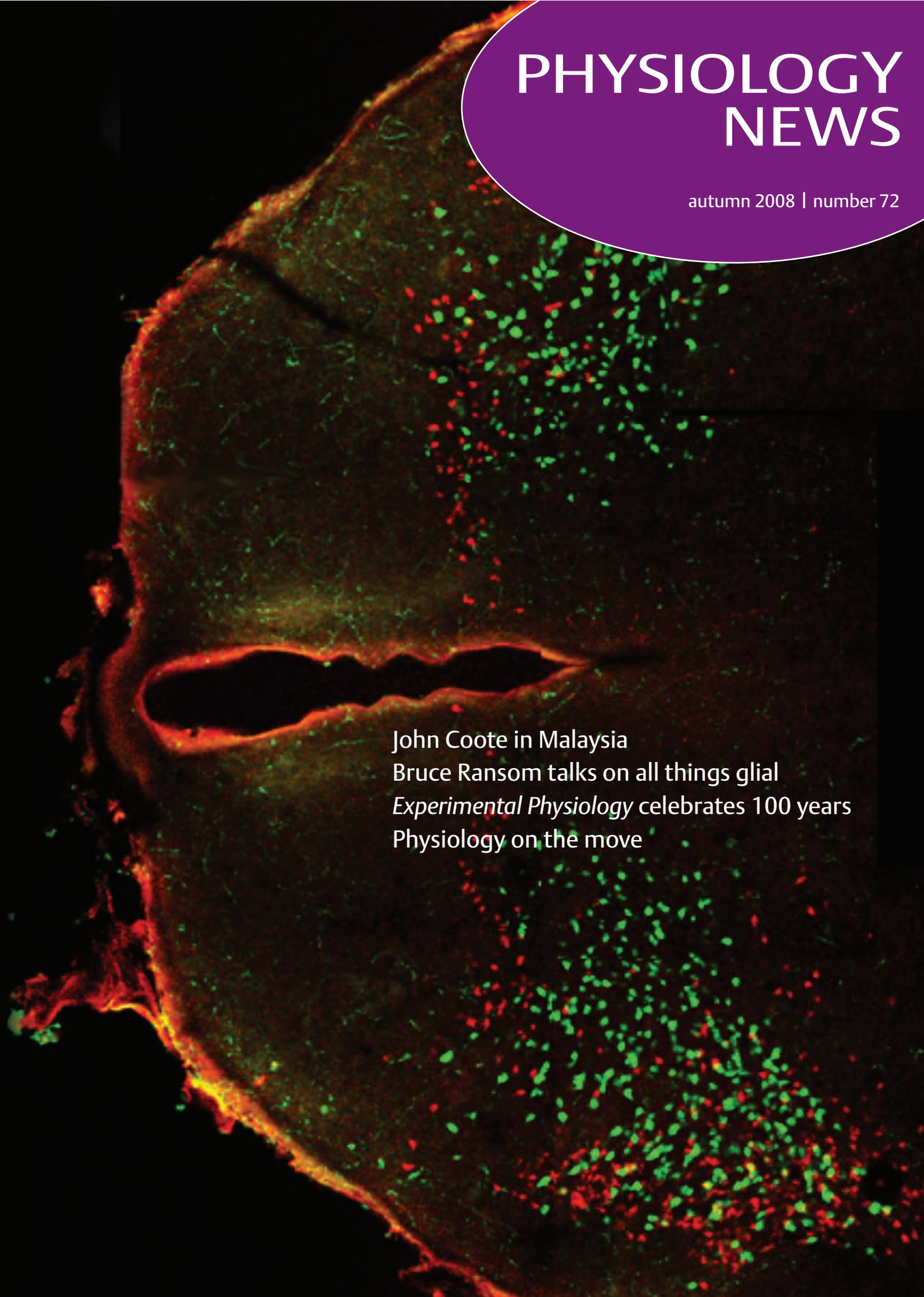
PHYSIOLOGY NEWS

autumn 2008 | number 72



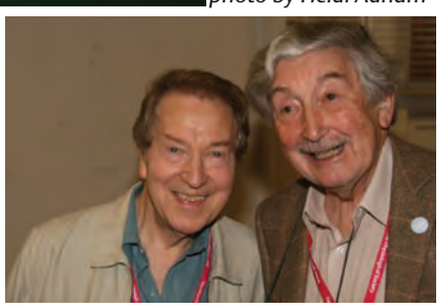
John Coote in Malaysia
Bruce Ransom talks on all things glial
Experimental Physiology celebrates 100 years
Physiology on the move

photo by Heidi Adnum

Physiology 2008

University of Cambridge, UK

14–16 July 2008



photos by David Eisner

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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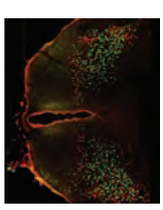

Cover image from *Orchestration of metabolism in health and disease*, p. 4

PHYSIOLOGY NEWS

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Action points

Grants
For full information on Members' and Affiliates' Travel Grants, Non-Society Symposia Grants, Vacation Studentship Scheme, Departmental Seminar Scheme, Centres of Excellence, Foreign Guest Scheme and Junior Fellowships visit:
http://www.physoc.org/grants

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Applications for Physiological Society membership are accepted throughout the year; applications are reviewed by the Membership Committee on a monthly basis and a decision is normally made within 15 working days of each deadline. For full details please visit:
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Please check and update your details at www.physoc.org, under 'My Physoc Profile'.

Physiology News

Deadlines

Letters and articles and all other contributions for inclusion in the Winter 2008 issue, No. 73, should reach the Publications Office (lrimmer@physoc.org) by **10 October 2008**. Short news items and letters are encouraged, and can usually be included as late copy if space permits.

Suggestions for articles
Suggestions for future articles are welcome. Please contact either the 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. Scientific articles should give a good overview of a field rather than focus entirely on the authors' own research.

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

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

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

Illustrations and authors' photographs
Authors are encouraged to submit diagrams, drawings, photographs or other artwork with their articles and a photograph of the author(s) should accompany submissions. Illustrations and photographs may be colour or black and white, prints, transparencies or tiff/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://jp.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

Welcome to the Autumn 2008 *Physiology News*. Summer and early Autumn is, of course, conference season. This year the Society has meetings in traditional locations (Cambridge and Oxford) and in places reflecting the 21st century scientific landscape (Beijing). It may be a bit fanciful, but this nicely reflects how I like to see physiology: a subject with a rich continuing tradition, but also with new horizons.

An interest in science is, for many scientists, more than just their career; it is a lifelong passion (obsession?). In keeping with this, for some people formal retirement just means more time to get on with the science. I spotted several eminent nominally-retired but scientifically-active older physiologists in the picture from the Cambridge meeting, and some people, like John Coote, seem to be busier in retirement than most people are in mid-career (see p. 7).

Whether this picture of the profession will remain so, given the increased difficulty for those who train in science in finding secure scientific employment, is one of the major questions facing science. On p. 40, Fiona Randall contemplates the end of her time as a PhD student, and weighs up the options.

Science progresses, in major part, by the opening up of new fields of study. As Bruce Ransom and Angus Brown discuss on p. 10, 40 years ago glia were just the boring bits of the mammalian brain that weren't neurones. Nowadays they are key players in brain activity, with their own journals and conferences. An example of modern glial research can be seen on p 18.

Austin Elliott
Editor

Peer review

Peer review, which lies at the heart of the scientific process, has a long history; the style of ('single blind') anonymous peer review now in common use was described by the Royal Society of Edinburgh in 1731, though the basic idea is far older. Despite this, widespread application of a system of anonymous expert referees did not become commonplace until later than is often believed, around the middle of the 20th century. Expert peer review in some form is now pretty much universal in scientific journals. So is there anything new to say?

Science vs non-science

One point that scientists sometimes need to remember is that peer review is not just important 'internally', but externally too. Properly functioning peer review is a key way to distinguish science from non-science (nonsense?). In a world where we are bombarded by apparently scientific claims – often for things that are being sold to us – it is important to have ways of telling sales talk and science apart, and peer review is one. As Sense About Science put it, peer review is an 'essential arbiter of scientific quality'(1).

A fly in this ointment, of course, is that there is peer review and peer review. Journals in the top couple of dozen, or possibly more, journals in established subject categories – such as 'physiology' – maintain rigorous review processes, as we all regularly experience. But there are a lot of journals, and reviewing standards vary widely. As a recent report for the Publishing Research Consortium puts it (2):

'Because the peer review standards of different journals vary, it is widely believed [by scientists] that almost any genuine academic manuscript, however weak, can find a peer-reviewed journal to publish it if the author is persistent enough.'

So, while publication in a peer review journal is some kind of quality mark, there is a blur at the edges.

Bibliometrics ... inevitably

One way we might seek to clarify the reliability of work published in peer review journals are journal 'pecking orders', nowadays often substituted by bibliometric rankings. The most common of these, journal impact factors (IFs), while derided regularly and with plenty of justification, are clearly here to stay. As The Physiological Society's journal editors put it elsewhere in this issue (p. 44):

'There is considerable divergence of opinion about the significance of [impact factors as a] measure of journal quality, but author surveys continue to confirm that a journal's IF is among the most important considerations in choosing where to publish.'

That is, impact factor is a proxy for pecking order, and thus perhaps, to a limited extent, for reviewing standards. This may indeed be the only thing for which journal IFs are useful, since their worthlessness in assessing individual scientists and their work has been attested repeatedly, including in these pages by David Colquhoun (3).

Of course, journal IFs are only useful even in this restricted fashion within subject categories; their inadequacies when NOT comparing like with like are well described. While general science journals like *Nature* and *Science* have far higher IFs than journals like *J Physiol* and *J Gen Physiol*, I have yet to meet a single scientist who thinks that the reviewing at the general journals is more rigorous. To take another example, comparative physiology journals have notoriously low IFs, though the technical quality of the work they publish is high.

Can we improve anything about peer review?

While peer review is clearly vital, it is also imperfect; I suspect there is no scientist alive who does not have some complaint to recount. To their credit, journals try hard to 'audit' their review processes, and to tweak them in ways that will help them work better. The latest fashion seems to be for more explicit instructions to reviewers as to how to assess a paper and write a reviewer's report. David Linden, the new editor of the *Journal of Neurophysiology,* has written about this recently (4), and *Nature Cell Biology* has also weighed in (5).

One thing I was glad to see in the latter was the exhortation to reviewers to ask 'Are all claims made supported by the data?' A personal view is that reviewers tend to be harder on whether they think experiments are technically correctly done – as *Nature Cell Biol* puts it: 'Are key experiments or crucial controls missing? Are the data significant and definitive?' – than on the inferences authors subsequently draw from the data. Though this is understandable, the danger here is that if an author repeats the same rather tenuous extrapolation in several published papers, they can then conceivably write a review citing all these papers and boosting tenuous extrapolation to the status of 'well-tested hypothesis' – next stop the textbooks. So a personal plea would be for reviewers to pay a bit more attention to what authors say in the Discussion, as well as in the Methods and Results.

This also brings me to a final point – what happens if you see a paper that clearly has something in it that is wrong, but that the referees have missed? It is certainly possible to write to the journal or its editors, though such letters rarely, in my experience, see the light of day.

My preferred solution to this problem is an electronic response thread following the online version of the article, something favoured by some medical journals and increasingly by exclusively online journals. While it is perfectly possible to pen a short review commenting on a paper or papers, this rarely happens either, mostly for 'activation barrier' reasons. Writing a review, even a short one, is hard work. In contrast, penning an e-letter is a lot easier, and in the best cases generates quite an informative online debate. It is a bit like seeing the reviewing happening live, except after publication, and sometimes shows up things the journal reviewers missed. Another recent *Nature Cell Biol* editorial reveals that response threads will be coming soon for the Nature Group journals (6), and it will be interesting to see who else follows suit.

So to peer reviewers out there: keep up the reviewing standards, watch the authors' extrapolations – and see you in an electronic response thread soon. Even after a few hundred years, this is no time to get sloppy.

Austin Elliott

1 Peer review". Sense About Science (http://www.senseaboutscience.org.uk/index.php/site/project/29).
2 Peer Review: Benefits, perceptions and alternatives. Publishing Research Consortium. (http://www.publishingresearch.net/documents/PRCsummary4Warefinal.pdf).
3 Colquhoun D (2007). How to get good science. *Phys News* **69**, 12–14.
4 Linden DJ (2008). Warm, fuzzy feeling. *J Neurophysiol* **100**,1.
5 Good review (2008) *Nature Cell Biol* **10,** 371.
6 What to publish? (2008). *Nature Cell Biol* **10**, 247.

Themed Meeting – *Orchestration of metabolism in health and disease*

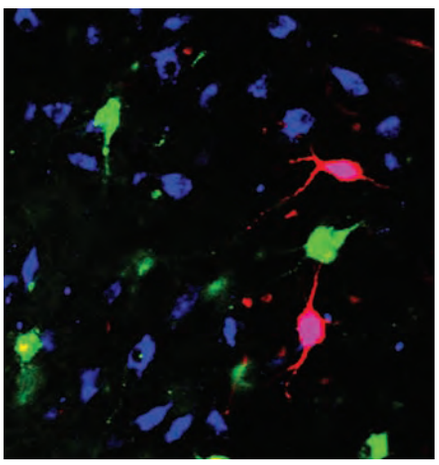
The University of Oxford will host the second Physiological Society Themed Meeting from Tuesday 9 to Thursday 11 September 2008 in the Medical Sciences Teaching Centre.

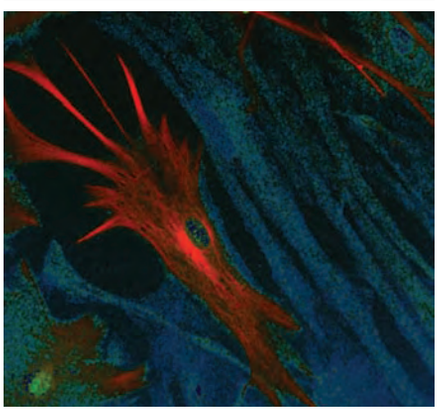
Metabolic disorders such as obesity and diabetes recently reached epidemic proportions worldwide. They now comprise the biggest clinical problem of the 21st century in terms of death toll from complications such as cardiovascular disease. No effective remedies currently exist due to the complex, multidimensional nature of metabolic regulation.

This Themed Meeting will bring together world leaders in basic and clinical disciplines related to metabolism and its malfunction, namely, control of feeding behaviour, sympathetic and cardiovascular sensing, and hormone release from the gut and pancreas. This unique multidimensional forum is an essential and timely platform for integrated understanding of metabolism.

Oxford itself, the 'city of dreaming spires', is famous the world over for its university and place in history. For over 800 years it has been a home to royalty and scholars and, since the 9th century, an established town, although people are known to have lived in the area for thousands of years.

A warm welcome awaits all those who have signed up to attend, or are planning to do so. Online registration closes on Monday 1 September so there is still time to come along to Oxford for what promises to be a landmark meeting bridging many experimental approaches to a key biomedical problem. Full details are available at http://www.physoc.org





From the top: Orexin, MCH and Nb-filled neurons (Burdakov Lab); Leptin receptor-expressing cells (Heisler lab and Sam Virtue); Sugar (Prem Kumar); Meeting venue in Oxford.

Speakers

Jeffrey Friedman
(Rockefeller University, New York, USA)

Frances Ashcroft
(University of Oxford, UK)

Steve O'Rahilly
(University of Cambridge, UK)

Jens Brüning
(University of Cologne, Germany)

Nina Balthasar
(University of Bristol, UK)

Mike Ashford
(University of Dundee, UK)

Stefan Trapp
(Imperial College London, UK)

Luis de Lecea
(Scripps Research Institute, La Jolla, USA)

Denis Burdakov
(University of Cambridge, UK)

Patrik Rorsman
(Oxford Centre for Diabetes, Endocrinology & Metabolism, UK)

Fiona Gribble
(University of Cambridge, UK)

Philipp Scherer
(University of Texas Southwestern Medical Center, USA)

Grahame Hardie
(University of Dundee, UK)

José López-Barneo
(University of Seville, Spain)

Prem Kumar
(University of Birmingham, UK)

Fred Turek
(Northwestern University, USA)

Mark Hanson
(Southampton General Hospital, UK)

Catherine Lawrence
(University of Manchester, UK)

Shahrad Taheri
(University of Bristol, UK)

Lora Heisler
(University of Cambridge, UK)

Rachel Batterham
(University College London, UK)

Joint Physiological Sciences Conference

Beijing, China 18–22 October

A previous article (*Physiology News* **59**, 10) summarised The Society's plans to host a 'joint' Physiological Sciences meeting in Beijing, China. Our Executive initially met with Tai Yao (President) and Xiao-min Wang (Secretary General) of the Chinese Association of Physiological Sciences (CAPS) at the IUPS meeting in San Diego in 2005 and then at the FEPS meeting in Bristol in July 2005. At the FEPS meeting, we further discussed the benefits of a joint meeting in Beijing in October 2008 and considered inviting the American Physiological Society to sponsor a designated symposium.

CAPS celebrated their 80th anniversary in November 2006 and invited Prem Kumar, Giovanni Mann, David Adams, Chen Chen, Shu Chien and Rui Wang as overseas guest speakers. Our hosts proposed that we extend an invitation to members of the American, Australian and Canadian Physiological Societies to join us for the Beijing Physiology 2008 meeting. The image (right, top) highlights our discussions with the CAPS Executive. Prem returned to London to discuss their proposal with our Executive.

Extensive email correspondence ensued and subsequently all agreed that representatives from the participating national societies should meet formally in Beijing in early January 2008 to plan the scientific programme, select a venue and consider sources of funding and sponsorship. Giovanni Mann attended on behalf of The Society, and we agreed that focused symposia would form the basis of the meeting with themes for symposia to be defined by each participating society. Over 20 different symposia were submitted and these were then rationalized so that each had invited speakers from two or more national societies.

Top: 80th Anniversary of the Chinese Association of Physiological Sciences (CAPS) in Beijing in November 2006. Prem Kumar and Giovanni Mann were invited as guest speakers and we agreed to extend the concept of a 'joint meeting' between CAPS and The Physiological Society to members of the American, Australian and Canadian Societies (left to right: Ming Fan, Prem, Tai Yao, Giovanni and Xiao-min Wang).

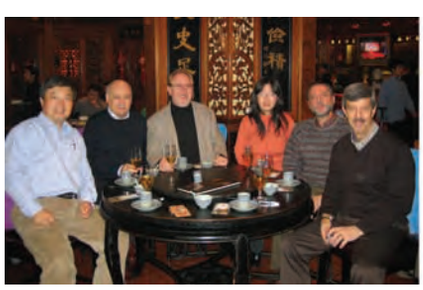
Above: Beijing Physiology 2008 scientific programme committee meets at Peking University in Beijing in early January 2008 (*front row*, *left to right*: Rui Wang (Canadian Physiological Society), Martin Frank (American Physiological Society), Xian Wang (CAPS), Tai Yao (CAPS), Ming Fan (CAPS), Chen Chen (Australian Physiological Society); *back row*, *left to right*: Doug Jones (Canadian Physiological Society), Ying-Shing Chan (CAPS) Giovanni Mann (Physiological Society), David Adams (Australian Physiological Society).

The success of our scientific programme meeting in January 2008 was borne out by the large number of participants, excellent symposia and free communications at the Beijing Physiology 2008 meeting. The agreement of national societies to support their invited speakers and younger affiliates really underpinned this ambitious venture! Special thanks are due to Mike Collis, Nick Boross-Toby, Liam McKay and all our staff in London and Cambridge who ensured that a professional website was up-and-running!

In addition to a wealth of international research, the Beijing Physiology 2008 meeting offers participants and accompanying guests a truly memorable cultural experience.

Denis Noble (Oxford) will give a Plenary Lecture on Monday 20 October on *Principles of systems biology from a physiologist's perspective*. The full programme, including 16 symposia, is available at http://www.beijingphys2008.org. On behalf of The Society and members of the Scientific Programme Committee, we welcome you to Beijing.

Prem Kumar
Meetings Secretary and Scientific Programme Committee
Giovanni Mann
Scientific Programme Committee



A memorable dinner with our lovely host from Peking University. David Adams, Chen Chen and Giovanni accompanied by the talented performer with multiple changing faces ... David, Martin and Doug with their local hosts. Definitely a venue worth experiencing not just for the special food but also for the amazing performances!

Physiology 2008

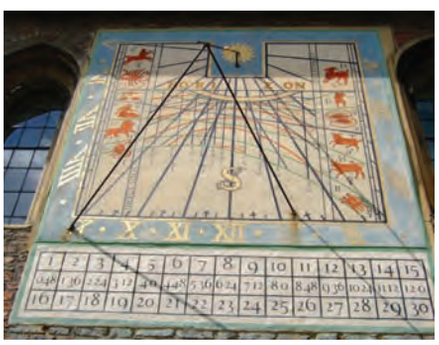
With the teasing prospect of some summer sunshine at last, The Physiological Society marquee was set up in the quad of the Downing Site to welcome 730 Members and visitors to Cambridge for the 2008 main annual meeting.

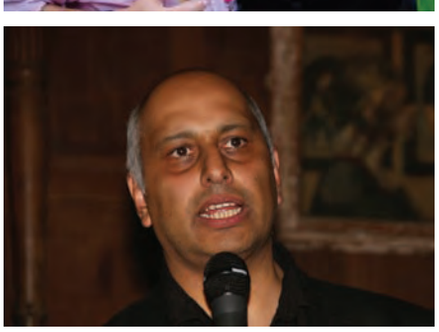
The meeting got off to a flying start, with a Young Physiologists' symposium and a Techniques Workshop the weekend before the main programme. Activities over the following 3 days reflected the extensive range of The Society's scientific interests, with 18 different research symposia on offer, as well as a teaching symposium and two careers sessions. In addition, there were 117 oral communications, 173 posters and five demonstrations, plus the trade exhibition.

Navigation through this impressive programme was relatively trouble-free as the abstracts were all available in advance via the meeting website together with some helpful software to generate a personal itinerary. Luckily, the meeting also offered plenty of opportunity to digest all of this scientific information over a glass of wine or two!

Cambridge, with its heady combination of picturesque colleges and scientific history, was a fine backdrop to these proceedings. The welcome reception on the back lawn of King's College was a delightful affair, with minstrels, a juggler and many glasses of wine. This was an appetiser for The Society dinners the following evening, which took place on two sites at King's and Queens' Colleges. All 400 or so diners enjoyed the same wonderful meal and hospitality, although those at the Queens' dinner will be sorry to have been denied the opportunity to hear Meetings Secretary, Prem Kumar, demonstrate his true vocation as a stand-up comedian!

The role call of plenary and prize lecturers during the meeting included some of the brightest stars of science at all stages of their careers. These lectures produced an examination of physiology in its complete sense, from understanding integrated systemic behaviour to the underlying molecular basis of function. The prize lectures punctuated the proceedings each lunchtime and evening, bringing the meeting participants together and facilitating subsequent discussions over sandwiches or more wine.





The AGM on the final day was well attended and generated debates on the merits, or otherwise, of a return to the former system of voting at meetings as well as the issue of registration fees. These discussions demonstrate the central importance of our scientific meetings and the Members' interest and involvement in this aspect of The Society. As scientists we are open to change, but also challenge its basis, and the AGM at the main meeting provides a forum for this debate.

So, congratulations to all those organisers and participants involved in making the Cambridge meeting such a satisfying fusion of science and socialising (and some sight-seeing, too). Here's to the next meeting in Dublin 2009 ...

Sarah Hall

More images of Cambridge on the inside front cover.

A full report of The Society's Annual General Meeting appears on p. 47.

For full details of Physiology 2009, the main annual meeting of The Society in Dublin from 6–10 July, visit www.physiology2009.org

A week in the life of ...

The things retired physiologists get up to. Flying troubleshooter John Coote has been getting sympathetic nerve recording going in Malaysia. When Thelma Lovick caught up with him recently, he was just back from a week in Penang, Malaysia

TL (Thelma Lovick) What took you to Malaysia?

JC (John Coote) I went there basically to help out one of my ex students. About 30 years ago Pauzi Yusof came to Birmingham to do a PhD with me. We were looking at 5-HT and its influence on vasomotor neurones. On his return to Penang, Pauzi became Head of his Department and for the past few years he has been Dean of the Faculty of Pharmaceutical Sciences. Obviously his time at the bench was severely restricted by these activities. However, once his term as Dean came to an end recently, he was keen to get back into the swing of things and to rekindle his longstanding research interest in autonomic control systems. Memories fade, especially regarding the technical details, and he was experiencing difficulties in getting things up and running again. So this is why he contacted me and I agreed to go over there for a week.

John Coote with Nurul Hashida (left) and Farah Wahida (right).

TL How did the week go?

JC Well, I arrived late one evening – about 10 p.m. There was a Government car waiting for me, courtesy of the Penang Prefecture, which whisked me off to my hotel. I then had a sleep and was picked up at 7.30 the next morning.

TL No time to get over jet lag then?

JC Absolutely not! I went straight in and at 8 a.m. we started our first bit of surgery.

TL What were the main problems?

JC Well, the labs are actually quite well equipped and they seem to have plenty of funding. But I had to reset most of their equipment. You immediately notice the little things that make all the difference to whether the experiment will work or not. They were trying to make stereotaxic injections of drugs into the hypothalamus but they didn't realise quite how much attention you have to pay to the fine details of setting this procedure up and so consequently it wasn't working. Ridding the recording system of electrical interference when monitoring activity in fine sympathetic nerves and the method for intrathecal catheter placement were just some of the other techniques that needed attention.

A prime lunching spot in Penang.

TL Did you have students standing by, waiting on your every word?

JC Yes, there were two students who were very, very diligent. When I got in at 8 a.m. each morning the animals were set up for me, so the students had arrived much earlier to prepare everything. We all worked through until about 6.30 in the evening each day. There was always a break for lunch for Pauzi and I, but not for the students though. We walked or drove to the edge of the Georgetown district where the University is situated, to a street with

Pauzi Yusof at work.

a row of run down-looking shacks with benches outside, each one serving pretty good food.

TL How long had these students been struggling before you arrived as the John Harvey Jones of physiology?
JC I suppose it must have been about 4 months.

TL So I imagine your arrival was quite welcome!
JC They hung on every word I uttered, and believed every word I said! It's very flattering, of course, but the good thing was that these two students were very intelligent young ladies. They wanted to get everything absolutely right – and they got the results. As well as the stereotaxic technique, I showed them placement of a fine catheter intrathecally to deliver drugs to the spinal cord, the placement of a catheter in the internal carotid artery to deliver drugs to brain and exposure and recording from the renal nerve. This is actually not that difficult when you know how, but unless you display the nerve well, it becomes more difficult. It's all in the detail. However, by the end of the third day, all of them, including my ex-student, were doing it for themselves.

TL And when you finished your 12 hour day?
JC At the end of the day, back to the hotel, time for a quick shower and then I was taken out for a meal at a fine restaurant!

TL Did you go armed with lots of kit?
JC I did take some things that I thought might be needed. Quite simple things actually. For example, I thought they might have been having trouble making decent pipettes for making microinjections deep into the brain so I took some of those. I also took some blue glass for making hooks for moving the renal nerve about. You can't use metal implements to move the nerve without damaging it, but if you use little glass hooks this does the trick. They need to be made of coloured glass though, or you can't see them under the microscope! In fact, finding a source of gas to provide a hot flame to melt the glass to fashion the hooks proved to be quite a challenge because there was no gas in the lab I was working in! Eventually we tracked down a microbiology department that had some gas and even a Bunsen burner to go with it and I demonstrated how to make the hooks. The Malaysians were both amused and delighted. It's actually quite satisfying when you produce a low tech solution to what had been a serious problem of maintaining nerve viability. It's also good for my morale that I am still able to successfully do the technical and surgical things in a lab.

TL Did you get any time for sightseeing – doing the tourist bit?
JC No, I'm afraid there wasn't time. I flew in, worked in the lab and flew out.

TL It sounds to me as if it was an enormous amount of work. You are, after all, supposed to be retired these days. Was it worth it?
JC Oh yes. By the end of the week they were getting really good results. In fact I have just heard that they are now getting data that is taking forward work that I started 20 years ago in Birmingham. The fact that I am retired from mainstream academia means that I can spend more time using my skills to train people. These days we aren't training enough people, in the UK or abroad, in *in vivo* skills.

TL Where is your next trip taking you?
JC I'll probably go to Beijing in October. I have an ongoing collaboration with a lab in nearby Tianjin University. In fact I spent a month there last year after my trip to Tibet to visit some labs where they're doing high altitude physiology, another of my interests.

TL Do you think you'll ever give up physiology and move on to pastures new?
JC I can't ever see that happening. When you think about it, physiology is really part of one's life. Everything you're doing, what physiological changes are occurring, it all raises questions. I've got some collaborations going on closer to home. One on autonomic control of heart function with Andre Ng and Kieran Brack at the University of Leicester is turning out to be very exciting and my work on sexual dysfunction in males is about to enter another phase when our new student starts in the Autumn (JC and TL have recently been awarded a Pfizer CASE studentship).

John Coote is Emeritus Professor of Physiology at the University of Birmingham, Birmingham, UK.

Control freak

Patricia de Winter finds some bad science out there and urges scientists to report their data accurately and publish responsibly

I recently read two articles that spurred me to write this piece, which concerns experimental controls and experimental design.

The first article, published in *Current Biology* (Inoue & Matsuzawa, 2007), was also reported by *The Guardian* newspaper under the headline *Chimps beat people in memory task*. The article was originally sent to me in an email from a technician who wrote 'it's official – chimps are cleverer than us!'. No it's not and they aren't – at least they might be, but nobody has demonstrated it yet – particularly not Inoue & Matsuzawa. Two points: first, the general public cannot necessarily discriminate good and bad science and, as our technician demonstrated, are likely to believe the hype written by *The Guardian*'s science correspondent and, second, the experiments were poorly controlled in the first instance and the conclusions are inappropriate.

Briefly, the experiments involved three immature chimps (aged 4 years) and their mothers. The chimps were taught to recognise the sequence of digits 1–9 over a year and then performed a series of touch-screen tests that involved memorising the positions of numbers and reproducing the sequence by touch once the numbers disappeared from the screen. The young chimps out-performed both their mothers and the controls, who were nine university students that had not been given the same length of training – the maximum was 6 months for three of the students – problem number one. Problem number two is that the researchers compared adult humans with immature chimps – chalk and cheese. The ability to retain an accurate, detailed image of a complex scene or pattern, known as eidetic imagery, occurs in up to 25% of human 5 year olds, but is very rare in human adults (Giray *et al.* 1976). Lastly, and perhaps most importantly, is the matching of the level of reward between the groups. The chimps were given a treat for completing each task but it is difficult, and I would say impossible, to determine whether the human subjects' reward (if any) provided the same level of incentive to perform the tests. Who's to say that offering a chimp a food reward is not the equivalent of offering a human a substantial amount of money – say a quarter of a million – wouldn't you develop an incredible memory with that carrot dangling in front of your nose?

The second article that I wish to criticise is one that I saw featured in *Nature*'s research highlights pages. It concerns the chick-feeding behaviour of *Parus major* (great tit) and caught my eye because I'm rather fond of birds. Birds, unlike humans, are able to detect ultraviolet wavelengths due to the presence of specialised retinal receptors, so birds that look dull to us may very well be perceived as brightly coloured to other birds. The original article to which I refer was published by Galván *et al.* (2008) in the *Journal of Avian Biology*. The authors coloured the feathers of a selection of *Parus major* chicks with a yellow marker pen to reduce their UV/blue reflectance and measured tarsus length (an indicator of growth) before and again 3 days later. Control chicks were measured but marked on the underside of the wing (not easily visible from above). Tarsus length was longer in non-manipulated chicks. There isn't a positive control in this experiment, but the other problem lies in interpreting the data. The authors suggest that nestlings with normal UV/blue reflectance, signal increased quality to their parents who consequently feed them more, as they are likely to be fitter. The experimental design does not permit them to come to this conclusion as they have not actually tested the relationship between chick fitness and UV/blue reflectance. All they have done is make the chicks less visible to their parents, so they get fed less frequently. It's not so much about chick quality as chick visibility. I asked my husband, an avian biologist, what he would do if this were his piece of research – apart from the positive control, he suggested returning the decreased UV/blue to normal and/or increasing UV/blue reflectance but, he says, it's still arguably all to do with visibility.

These are not physiology papers, and as a rule physiologists are pretty good at experimental design. Perhaps it was all those years of presenting papers to an audience that would vote on whether your paper was accepted for publication that spurred physiologists to ensure that only top-notch science was presented at Society meetings, and the memory of it hasn't faded yet.

But there is clearly some bad science out there, and I believe that scientists have a responsibility to report their data accurately and publish responsibly. What we publish can have an impact on how science is perceived by the public, and can also have huge social implications as the case discrediting the link between autism and MMR vaccine clearly showed.

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All things glial

On a recent trip to Seattle, Angus Brown took the opportunity to catch up with Bruce Ransom (right), one of the founding fathers of modern glial research

AB (Angus Brown) Your first paper in 1973 was titled *Ionic determinants of membrane potential of cells presumed to be glia in cerebral cortex of cat*. Was it typical of the state of glial research of the time that glial cells were essentially classified as a single entity, and were classified by what they could not do (generate action potentials) rather than by their own specific properties?

BR (Bruce Ransom) Yes, you are absolutely right in stating that we had a foggy notion about the physiology of glial cells at that time. Very clearly they were most recognizable by the things they couldn't do, by the things they didn't have – action potentials, synaptic potentials, etc. The specific astrocyte marker, Glial fibrillary acidic protein (GFAP), had just been discovered and would usher in the ability to accurately discriminate astrocytes from oligdendrocytes. But from a physiologist's standpoint, especially trying to look at glial cells *in situ*, there really was no way to identify one glial cell type from another.

AB So if you stuck an electrode in a cell and it didn't fire an action potential it was presumed to be a glial cell, if it had a decent resting membrane potential?

BR That is absolutely correct, and to be on the safe side we referred to these cells as 'presumed glial cells', as we wanted to recognize that there were rare neurons, as in the retina, that did not fire action potentials. There was a strong presumption that our cells were glial cells, but I would not have been able to identify them as astrocytes or oligodendrocytes.

AB Could you give us a brief history of glial research from the original definitions by Virchow etc. up until you started your research in the early 1970s?

BR I can certainly take a stab at that. The era of Virchow's discovery, which is the mid 19th century (1858 is the year he published his first illustration of glial cells) was purely a period of histological research. There was virtually no physiology. Virchow was a pathologist; he was strongly committed to the notion that every tissue had to have inflammatory cells. That was a powerful concept at the time in pathology. So he looked hard for such cells in the brain and what he was able to see in crude histological preparations were neural cell bodies, and between these elements there appeared to be small corpuscles or amorphous material, which could have been either a special form of intracellular matrix, or cells or both. This is what his pictures basically described. Looking back now at his illustrations it is very difficult to say what it was precisely he was looking at. My colleague Helmut Kettenmann, a German and a real student of neurobiology history, has read the original German descriptions by Virchow and comes away with the impression that Virchow himself was not completely certain if these were cells or some kind of intercellular matrix. He gave this material the name 'neuroglia', roughly nerve cement or nerve glue. So that's the beginning.

Things sat almost unchanged for about two decades before the start of the great glory days of neuro-histology propelled by Cajal, Golgi, and a large number of Germans – Henle, Weigert, Bergmann, His – there's a long list. After the discovery of Golgi's fantastic 'black reaction' we could begin to selectively, but capriciously, stain in their entirety both glial cells and neurons, and at that point astrocytes came into full view. These non-neuronal cells were referred to by many descriptive names, including spider cells. The word astrocyte itself was introduced by Lenhossek, a German, in 1893. Further refinements of this histology followed, provided mainly by Spanish and German workers, and included clear definitions of oligodendrocytes, astrocytes and microglial cells. But beyond the realization that oligodendrocytes provided myelin, no real insights into glial cell function emerged. Finally, beginning in the 1960s some serious physiological studies were undertaken on these cells. Of course, the pace of work on glial cells lagged pathetically behind research on neurons. There were no electrical signals, like the action potential in neurons, that distinguished glial cells and could be used to interpret their functions. They were still viewed basically as neural-scaffolding, a kind of structural element and nothing more. So there was not only little ability to study them, but also little interest in studying them. Studies began to appear showing that cultured glial cells, mainly astrocytes, could respond with membrane potential changes to some neurotransmitters; these were purely descriptive studies, but at least they disturbed the prevailing dogma and suggested that these cells might be more interesting than we'd given them credit for. I recall reading one such study very carefully when I began my graduate work in 1969. It was very primitive. Now this state of affairs was something that bothered one of my scientific heroes, Stephen Kuffler. Stephen Kuffler was a renowned neuroscientist who had already made a number of extraord-

inarily important contributions to spinal cord physiology, to retinal physiology and to sensory physiology. He discovered surround inhibition, presynaptic inhibition, and the receptor potentials in sensory neurones. He decided in a way that almost became his calling card to get into a completely new field. He set off on a quest to find a preparation that would permit him to make discerning studies of these elusive cells, physiological studies, and he hit on two preparations: the amphibian optic nerve, which is of course a part of the CNS and very easily obtained, and the leech CNS. Using these two preparations he and his colleagues – John Nicholls, David Potter and Richard Orkand – published several monumental papers on glia. From these studies, we learned that glia had high negative membrane potentials, were selectively permeable to K^+, were electrically coupled by gap junctions and sensed nearby activity in neurons by the K^+ they released. This work narrowly defined glial cells. I say narrowly because there were a number of things that they had not bothered to investigate, such as whether there might be neuro-transmitter receptors on these cells. They didn't wildly speculate that there may be some interaction with neural transmission or neural signaling and, in fact, when they wrote their large review article, they spent quite a bit of time debunking some of the idle speculation that had taken place previously, such as glial cells were involved in providing nutrition, they found no evidence of that in their studies. This was unquestionably the beginning of modern glial physiology.

AB Your mentor in those days was Sidney Goldring. What influence did he have on you?

BR Sidney Goldring was a neurosurgeon at Washington University in St Louis whose surgical interest was primarily the resection of epileptic foci in people with intractable epilepsy. He had very carefully read Kuffler's work and he had made some early recordings of cortical neurons *in vivo* using intracellular microelectrodes, where he had encountered inactive cells with high resting membrane potentials. He discovered that when the cortex was repetitively stimulated with surface electrodes these cells would slowly depolarize. He was very excited about that because he had previously used DC recording techniques to discover that repetitive stimulation of the brain not only produced action potentials and evoked potentials, but also slow negative potentials that lasted many seconds, and there was a lot of debate about what these slow potentials might be coming from.

AB Was this distinct from spreading depression?

BR This is completely distinct from spreading depression. These were transient potentials associated with completely normal neural discharge, but they went undetected if you used AC coupled recording techniques, which were, of course, the norm. It was a passion of his to try to explain this on a cellular basis, and these cells that he would rarely encounter with high negative membrane potentials, would depolarize with exactly the same time course as these slow negative potentials, offering a pretty good physiological explanation. Kuffler's physiological definition of primitive glia gave him a great opportunity to test whether his mammalian 'silent cells' might also behave as potassium electrodes. Are they low resistance cells and do they depolarize to nearby neural activity? So I began a series of experiments in cat cortex following the recipe set out by Kuffler in invertebrate preparations. I was left, at least for the first several months, flailing about in the lab trying to make useable intracellular micro-electrodes, very difficult at that time, and I went through a dark period trying to figure out how to do these experiments. Fortunately Washington University had an excellent neurobiology group, including Carl Rovainen, who was a student of Kuffler's. Carl was a gifted electrophysiologist skilled with intracellular recording techniques, and he was an important influence on me during my graduate student days. Sidney Goldring provided a distant but important kind of encouragement, supported me completely and set me on the path of my glial studies. He held me accountable and he presumed that I would be self-motivated and would have the good sense to find answers to my questions in this wonderful environment.

AB Was there ever a problem getting glial research published in what I presume was a neurocentric world – were journal editors receptive to glial research or were they still skeptical?

BR I think there was a lot of skepticism. In 1966 Kuffler and Nicholls published an incredibly exhaustive review of neuroglial cells, and in that review they took issue with some of the idle speculation about these cells and criticized some of the techniques that had been used to study glial cells. They summarized their own work on invertebrate glia and established the validity of studying these brain cells. At the same time they were highly critical of much of the glial research that had been done up to that point. So I thought it nicely articulated the scientific frame of mind of that era – 'Yes, glial cells are real and important, but you must bring us legitimate, carefully done research, or we're frankly not very interested'. So there was a threshold that had to be overcome to get your work into legitimate journals. You had to really bring carefully done work using modern techniques. Talking about glial cells in ground up tissue based on the notion that 40 to 50% of the tissue might be glia was no longer acceptable to the best journals. Things obviously evolved, but rather slowly, after the Kuffler period.

AB Was this the impetus for you to found the journal *GLIA*?

BR This idea came to me in 1986, and then Helmut and I pursued it and we published the first issue of *GLIA* in 1988. This was 15 years since I'd published my original work on

glial cells, and there was a blush of optimism that glial cells were far more interesting than we'd originally thought, that they may indeed be expressing neurotransmitter receptors; that they might interact in interesting ways with neurones. There were some early studies demonstrating that astrocytes were the sole cells in the nervous system with glycogen, causing speculation that the glycogen might be an energy reserve for the glial cells, and perhaps for its neural neighbours. There were a lot of interesting ideas floating around, and I and my colleague Helmut Kettenmann were absolutely certain that these cells would prove to be extremely important in the nervous system. We were concerned that the literature about these cells was very fractured. There was no one place where you could look to kind of get a mainstream notion about what was happening in glial research. Our timing in that regard could not have been more perfect. There was a real need for *GLIA*.

AB Could you highlight a few of the most memorable contributions to the field of glial research?

BR I have already emphasized the importance of the Kuffler work. It was terribly important to extend the invertebrate picture of glial cells provided by Kuffler and his colleagues to the mammalian world, and I am proud to say that I had a hand in that, with my thesis work, published back in 1972.

I published three linked papers in the *Journal of Neurophysiology* and the 4th in *Brain Research*, looking at the basic properties of glial cells in living cat cortex. This was difficult work but I was fortunate in being surrounded by people who were able to help me with the technical difficulties that I encountered. This work validated that mammalian glial cells could be readily identified and studied. The behaviour of these cells was such that one could surmise that they were very likely coupled to one another and, in later work, Barry Connors, Mike Gutnick and I were able to demonstrate that indeed they were coupled through gap junctions. Helmut Kettenmann's early work using careful tissue culture techniques to look at various types of glia was crucial to proving that these cells expressed numerous neurotransmitter receptors, at the time a heretical concept. This was an extremely important observation and I think it put the neuroscience community on notice that these cells were complex and could no longer be ignored.

Subsequently, a lot of details were filled in, and a very exciting chapter unfolded during development. This has been pursued by a number of different labs, showing that glial cells are involved in aiding neurones in their movement to correct positions in the cortex, radial glial cells are particularly important in this. Glial cells are now even involved as stem cells for the production not just of other glial cells but of neurones also. Axon guidance involves glial cells, and glia secrete molecules during vital times during development that help guide emerging axons to their correct positions in the CNS. I would also like to acknowledge the work that you and I collaborated on together, that is the role of CNS glycogen. There had been a lot of speculation about the role of glycogen dating back to its discovery, and early characterization involving people like Oliver Lowry and his colleagues, but no evidence showing how the glycogen was used. I really believe that our work was instrumental in pointing to the fact that the breakdown product of glycogen provides energy substrate not just for the astrocyte, but for its neighbouring neurones and axons under conditions of intense neural activity and certainly under conditions of glucose starvation. The role astrocytes play in providing a precursor for the manufacture of glutamate and GABA is also very important, as well as their role in removing glutamate and GABA following synaptic release. Finally, there are important recent studies showing that neurons and glial cells interact during synaptic processing in a way that suggests glial cells are involved in integrating information. There are many more extremely important highlights that could be mentioned related to oligodendrocytes and microglia but listing these would test your patience.

AB You are renowned for your work on central white matter injury, which has implications in such conditions as spinal cord injury, lacunar infarcts, multiple sclerosis and stroke. Why do you think there has been such a relative lack of success in therapeutic applications of stroke research – do you think it could be an underestimation of the contribution of white matter?

BR Yes, I think that there is overwhelming evidence in favour of that conclusion. The vast majority of research on the cellular mechanisms of ischemic injury has been done on rodents. Rodents have a useful nervous system for testing hypotheses about stroke injury, but they have a huge disadvantage, which is primarily that only about 10 % of the rodent CNS is white matter. So the injury you are looking at in a rodent that is delivered by a standard period of vascular occlusion is almost exclusively a grey matter injury. In the human brain, by contrast, at least 50 % of forebrain volume is white matter. We know from simple pathology studies that white matter is involved in virtually every stroke a human being suffers, and in about 25% of strokes, referred to as lacunar infarcts, the damage is almost exclusively to white matter. So our over-reliance on the clues we garnered from studying rodents led to a series of pharmacologic misadventures in human stroke trials. In rodents, NMDA blockade produces tremendous neuroprotection, but in humans we have found over and over again that there is no significant clinical improvement in humans who receive an NMDA blocker shortly after their stroke. I am convinced that a major reason for this is that NMDA blockade has no benefit whatsoever for white matter. So I think that's an incredibly powerful insight that it took us an embarrassingly long time to discover.

AB And about $1 billion of NIH funding.

BR I don't know how much NIH funding, but certainly millions of dollars, but if you look at major Pharma, the estimates are in excess of $20 billion that were now, in retrospect, mis-spent on NMDA type trials.

AB I am introducing a 10 credit neuroglia module to our final year neuroscience course in Nottingham comprising about 10 lectures. Any advice?

BR Well I couldn't be happier to hear that, and I completely endorse the notion that it is now legitimate to have a full course on glial cells. That would have been an unthinkable thing even 15 years ago. I think that this is very sensible, it will allow you to build a solid background on the fundamental characteristics of glial cells over 3–4 hours of lecture, and by that I mean the subtypes of glial cells, their developmental history and the fine points of their histology. There is a lot to discuss about the anatomical features of astrocytes, oligodendrocytes, microglial cells, glial cells during developments, the emergence of the different forms of glial cells, the persistence of certain stem cells and the life history of glial cells. This could all be thoroughly dealt with over 3–4 hours of discrete lectures before moving to a full discussion of their physiological characteristics and functions. There's a lot to discuss about the biochemistry and metabolism of glial cells, the complex story about oligodendrocytes and axon myelination and finally, the pathologic involvement of these cells in different diseases. You will have no problem coming up with 10 hours of lectures, and I haven't even mentioned microglia, which is one of the fast emerging areas in CNS pathology. So I have no doubt that you'll easily fill your lecture schedule with lots of hard science about these cells, and you can end on the note that there is going to be a whole lot more to come.

AB As one of the key founding fathers of modern glial research you must be very proud that so many of the scientists you have trained in your laboratory have gone to the four corners of the globe and continue this research, and also the tremendous pace of glial research, which must have been inconceivable when you first started.

BR Yes, that's all true. I've been absolutely blessed with opportunities to work with exceptionally talented young scientists, primarily as postdocs in my lab when I was at the NIH, Stanford, Yale and now at the University of Washington, and it is tremendously gratifying to see all of the things that these individuals have accomplished. If there's a single thing about which I'm proudest it is the fact that I have had the chance, to perhaps have a little influence at formative moments in the lives of these young scientists. There is great satisfaction in that.

As to the emergence of glial research as extremely important, almost glamorous, I would have to say, frankly, that I am not surprised. I was absolutely certain that this would evolve. I didn't predict that it would have moved with the energy that it has, but I was pretty darned sure that I had it right back in 1988 when I took the plunge with *GLIA*. You'll remember that in the first year of *GLIA* we barely managed to publish 300 pages. Now we could publish 4000 pages if we wanted to, although we're holding the line at about 2000 text pages a year. And glial articles are appearing in every major journal – *Science*, *Nature*, *Neuron*, *Journal of Neuroscience* ...

The pace of progress in this field is amazing, and I couldn't be happier about that. If I were going to offer an explanation it would partly be that the function of the nervous system, the most complex biological organ, is now clearly recognized as a collaboration between neurones and glial cells, and I think that everyone realizes today that we're still playing catch up in glial research. It will be a further while before we have an equivalent amount of information about glia to complement the tremendous backlog of information that we have about neurons. And until we have just as much information about the glial cells as we do about the neurones, we'll never be able to solve the phenomenal jigsaw puzzle of how the brain works.

The Physiological Society Benevolent Fund

The Fund exists to help anyone who 'by the nature of their employment can be considered to have contributed to the advance of physiology' and who is in 'necessitous circumstances'. This means not just physiology departments, but also other departments and institutes which help advance physiology; and it means not only academic and research staff but also includes anyone who has worked to support physiology, whether as a technician, porter, cleaner, etc. There are many ways in which the Fund can be used to help beneficiaries. Examples include grants (or loans) towards funeral expenses, emergency travel, medical costs, childcare arrangements, relocation costs and unexpected bills.

For further information and applications please contact Liz Bell (ebell@physoc.org or telephone 020 7269 5711).

The Benevolent Fund annual raffle, which took place at The Society meeting in Cambridge in July, raised £313. The prize went to James Trimmer of the Department of Neurobiology, University of California Davis.

Sixth meeting for academic project licence holders and deputies

The 6th joint Home Office, Universities UK and Biosciences Federation meeting for academic project licence holders and deputies takes place on Thursday 9 October at the Home Office in London.

The meeting programme is aimed at all project licensees, deputies and those soon to become project licensees. Please note that there will be two parallel afternoon workshops designed for participants of different experience.

http://www.bsf.ac.uk/asg/asghome.htm for further information. Closing date for registration is 29 September.

Is there a case for the word 'homeotaxy'?

A commentary on Andrew Packard (2006). Contribution to the whole (H). Can squids show us anything that we did not know already? *Biology and Philosophy* **21**, 189–221

It is not every day that a new word enters the scientific vocabulary. However, in his essay Andrew Packard discusses 'wholes' and 'parts' – that is, how the organism behaves as a whole and not as a collection of parts – and sets out to explore whether there is the need for a word to describe the situation where a group of cells functions as a physiological syncytium – that is, co-operates in the absence of central control.

He proposes the word 'homeotaxy' – literally, the same arrangement – but which Packard calls, peer conformity – that is, cells acting in the same way as their adjacent cells. He assumes these cells are in the same physiological state and contrasts this situation with cell division and differentiation which he calls a hierarchical or vertical process. In this process the cell acts as a unit in contrast to the situation where a group of cells functions as a single unit.

As an example of a horizontal or non-hierarchical process he selects the skin of a squid, Loligo vulgaris, and its continued ability to function as an entity following denervation or removal of any hierarchical process. There are many examples of such tissues or organs in the animal kingdom, including hearts and various parts of the intestinal, urinary and reproductive systems. Packard specifically quotes a number of invertebrate myogenic preparations, including electrical conducting epithelia in sponges and involution in jellyfish due to the spread of electrical waves along ectodermal layers to the endoderm and epithelio-muscular layers through the mesoglea. The vertebrate and molluscan hearts are particularly good examples of horizontal control in which they can continue to contract for long periods when isolated from the whole organism or when denervated, both

Andrew Packard.

conditions where central or vertical control is absent (some primitive fish hearts even lack an innervation). These organs are referred to as having myogenic properties (peripheral automaticity), as is the situation with the squid skin. However, Packard considers the squid skin preparation is a visually striking example of homeotaxy with its detailed patterns of connectivity associated with the contraction and relaxation of the chromatophore muscles. However, I am not convinced it shows us anything that cannot be found in other myogenic tissues, though I agree these are less visually attractive.

What is the mechanism whereby a group of cells function in a homeotaxic fashion? There are a number of possible mechanisms which have been proposed and Packard refers to these. They include an electrical field, a wave of intercellular calcium signalling, extracellular matrix and electrical coupling. Permeable junctions allow small molecules, such as cAMP, to pass from cell to cell to cause homeotaxy. In the case of the vertebrate heart there is specialized muscle, the pacemaker, whose cells have the fastest intrinsic activity (due to spontaneous depolarization), leading to a wave of muscle contraction and a coordinated heart beat via gap junction connexin channels. In the case of the squid, central control can mask the coupling between the skin cells. Another form of horizontal control is the 'community effect' first observed in embryonic mesoderm cells.

In conclusion Packard makes a reasoned case for a specific term to denote cooperation between a group of cells functioning as a physiological syncytium, and homeotaxy is an acceptable word. However, the word homeotaxy fails to provide any indication regarding the mechanism responsible for this phenomenon. Packard concludes that several mechanisms operating in parallel are likely to be involved in homeotaxy. In this age of molecular biology, Packard presents a thought-provoking essay and I recommend the reader to it, though the text requires reading more than once to fully appreciate it and I have not considered all aspects of the essay. This is a scholarly and well argued essay the contents of which are backed by an extensive reference list spanning almost 100 years.

Robert J Walker
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John B Gurdon (Wellcome Trust/Cancer Research UK, Cambridge) comments:
As Robert Walker has indeed noted, Andrew Packard's concept has some clear relationship to what we described a while back as a community effect. Therefore I am very glad to know about Andrew Packard's ideas.

Robert Walker indicates that a mechanism for the phenomenon described by Andrew Packard is not known. In the case of the community effect, we proposed that it operates by the concentration of an extracellular molecule, in this case one of the FGF members.

It will be particularly interesting if it is possible to come up with hypotheses regarding the basis of the Andrew Packard phenomenon and to test these in a living system.

The lymphatic pump – from oedema to envenomation

The lymphatic pump has a key role in tissue fluid homeostasis. Nuclear medicine techniques provide a relatively safe means to investigate lymphatic function, including the pump, in humans. The pump is capable of generating high pressures (as high as diastolic blood pressure), and chronic failure of the pump in lymphoedema of the arm in breast cancer patients may account in part for the swelling

Oedema develops when capillary filtration exceeds the capacity of the lymphatic drainage system for a substantial period. Oedema is a familiar medical condition, whether it be the dependent oedema of the feet, the angioedema of allergy, the pulmonary or systemic oedema of cardiac failure (hyperfiltration oedemas), or the chronic (lymph) oedema occasioned by lymphatic insufficiency. What do we know of the lymphatic side of things? Starling, writing on the movement of lymph in his short textbook of human physiology in 1892 (and doubtless drawing on Heller's work some 20 years previously) referred to lymphatic vessels as channels with rhythmically contracting muscular sacs and valves that pump lymph (Starling, 1892). He discussed the significance of pressure gradients, active and passive limb movements, and noted the low to zero flow in the resting limb.

Cannulating lymphatics

Moving on almost a century, Olszewski & Engeset (1980) recognised that peripheral lymph propulsion was poorly characterised and addressed the question 'How is lymph propelled along the peripheral lymphatics of humans?' Subcutaneous lymphatic vessels draining the foot and anterior lower leg were cannulated in healthy men and, with the cannula left *in situ*, lymph flow and pressure were measured a few days later. With the subject supine and the cannula connected to a pressure transducer with flow obstructed, pressure pulsations were recorded with peaks usually in the range 12–55 mmHg, but occasionally much higher (120 mmHg). Standing up increased pulse frequency (Fig. 1). With free flow of lymph, peak pressures were lower (7–30 mmHg) and flow averaged 0.25 ml h^{-1}, rising 6-fold during a pulse wave. Foot and leg movements did not increase the peak pressures but did increase the frequency of pulsation and flow, which appeared to be linked. Lymph flow occurred only during the pressure pulsations. This excellent study thus established that human prenodal lymphatic collector vessels in the leg contract rhythmically to propel lymph centrally. Interestingly, by artificially raising the intraluminal pressure, spontaneous contractions were evoked. The authors also thought that extrinsic skeletal muscle contractions facilitated flow by increasing lymph formation (capillary filtration and lymph flow are closely coupled) and by an external pumping action on the non-contractile initial lymphatics.

Simulating envenomation

The above approach, involving surgical cutdown, was invasive and cannot be used ethically to study patients. Over the past 20 years or so less invasive techniques have been developed, based on gamma camera imaging of lymphatic transport. Howarth *et al*. (1994) used this approach to see what tourniquet pressure is needed to halt lymph drainage during the first-aid treatment of snake or spider envenomation. They simulated envenomation by injecting a radiotracer (^{99m}Tc-antimony sulphur colloid) intradermally or subcutaneously in the ankle or wrist and measured the transit time to the regional lymph nodes and the systemic circulation. Pressure was applied to the limbs by bandaging proximally from the depot, initially with the limb immobilised and the subject supine. Bandage pressures of 55–70 mmHg held for 30–145 min prevented radiotracer transit from ankle to inguinal nodes in most subjects; pressures < 55 mmHg did not prevent transit and a pressure of 90 mmHg for 35 min did not prevent transit in one subject. In the arm, pressures as high as 85–110 mmHg applied for 25–45 min (and causing numbness) failed to prevent transit

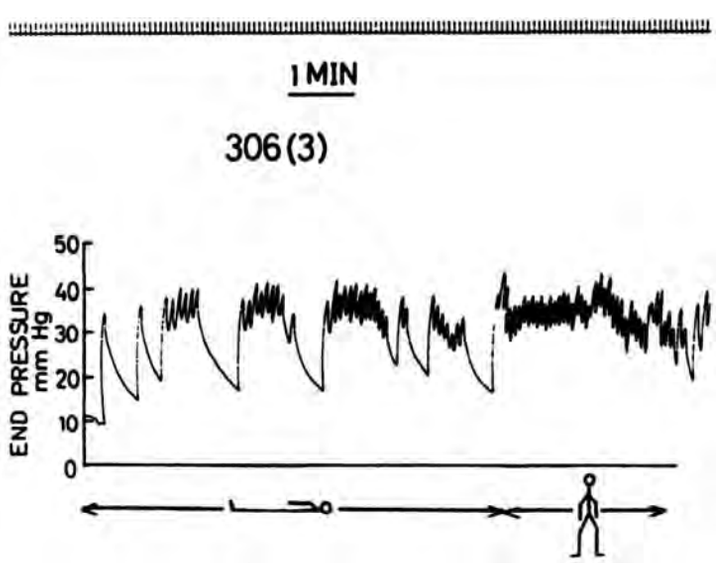


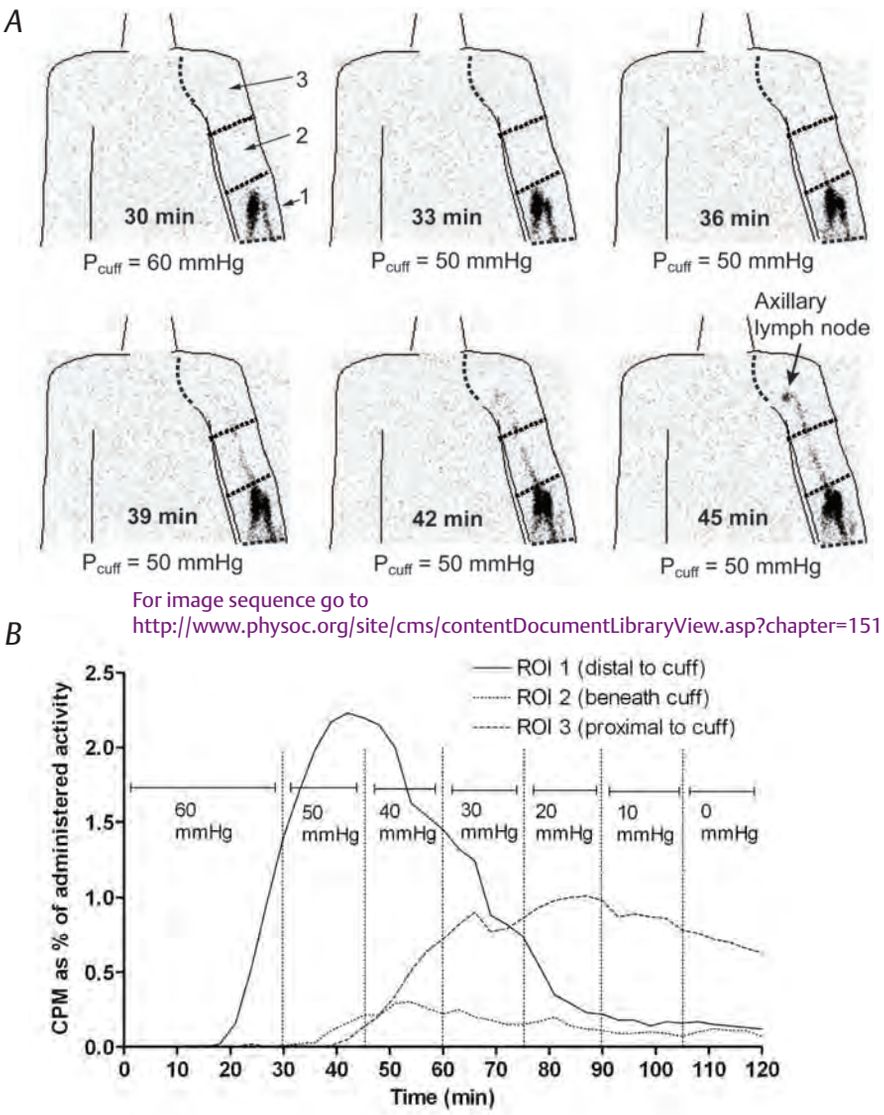
Figure 1. Pressure recording from a cannulated leg lymphatic of a healthy volunteer. The cannula is temporarily obstructed and the end-lymphatic pressure recorded. Pressure pulsations occurred whilst lying down, with peaks in this case reaching 40 mmHg, but occasionally reaching 120 mmHg. Standing up increased the frequency of pulsation, but did not increase mean pressure of the pulsatile phase, despite higher lymph formation rate expected in the upright position (from Olszewski & Engeset, 1980, reproduced with permission).

from wrist to axilla in 6 of the 15 subjects; 40–70 mmHg was effective in just under half the subjects. Exercise promoted transit. The findings of Howarth *et al*. thus reinforce the findings of Olszewski & Engeset (1980) that human limb lymphatics are capable of powerful contractile activity.

Probing the pump in lymphoedema

In recent years, exploration of lymphatic function in humans using nuclear medicine techniques has focused on the arms of women treated for breast cancer. Damage to the lymphatic drainage paths running through the axilla by the surgery or radiotherapy often results in a delayed, disfiguring arm swelling called lymphoedema. Using a development of Howarth's approach, Modi *et al*. (2007) assessed lymphatic contractility in healthy control arms and in the lymphoedematous arms of women treated for breast cancer. Their technique, called lymphatic congestion lymphoscintigraphy (LCP), employed a mercury sphygmomanometer and Riva-Rocci cuff to apply pressure around the upper arm. By injecting radiotracer (^{99m}Tc-IgG) intradermally into the hand of the supine subjects and gradually reducing the cuff pressure whilst imaging the upper arm and axilla, the pressure that the forearm lymphatic collectors could overcome (the 'pump pressure') could be established (Fig. 2). The aim was to explore the idea that, following surgical excision of axillary lymph nodes, lymphoedema occurred because of impaired intrinsic contractility of the superficial collector lymphatics in the face of chronically increased resistance to flow downstream.

In the *absence* of cuff compression, transit from the hand to the axilla was found to be remarkably fast, < 3 min in one subject and the longest time was 21 min. With the cuff in place in healthy individuals, the radiotracer flowed up the forearm and under the cuff to reach the axilla at an average cuff pressure of 39



For image sequence go to http://www.physoc.org/site/cms/contentDocumentLibraryView.asp?chapter=151

Figure 2. Lymphatic congestion lymphoscintigraphy – gamma camera images (*A*), and plot of activity (CPM, counts per min) in three regions of the arm (*B*), following injection of ^{99m}Tc-HIG in the hand of a healthy volunteer. When the pressure of the cuff (P_{cuff}), positioned over ROI 2, is lowered from 60 to 50 mmHg, activity begins to travel under the cuff, eventually reaching the axilla 45 min post-injection. P_{pump} is ~50 mmHg. The plot shows the substantial rise in forearm (ROI 1) activity before P_{pump} is reached, and the later rise in activity in ROI 2 and 3 (from Modi *et al*. 2007, reproduced with permission).

mmHg, but at higher pressures the radiotracer could not get past the cuff. Thus, the mean lymphatic collector pump pressure was 39 mmHg, though with a wide range (10–60 mmHg). Blood accumulation of tracer increased sharply after the tracer reached the axilla, as the radiolabelled lymph progressed to the thoracic duct and entered the great veins, with a further surge in blood counts when the subject later stood up and moved around.

In lymphoedematous arms the pump pressure was significantly impaired, averaging 24 mmHg. An image sequence showing the progression of activity up the arm in one patient is available at the above address.

The range of pump pressures was again wide (0–60 mmHg) and the pump pressure correlated with the degree of swelling (Fig. 3). The overlap of pump pressures with the healthy arms may indicate that additional factors besides impaired pump contractility contribute to the lymphoedema. The blood surge after the axilla was reached was less marked, in keeping with impaired

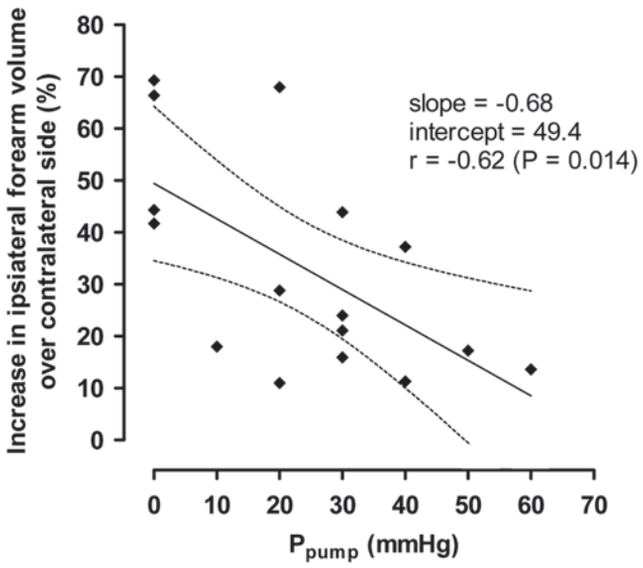


Figure 3. The relationship between the percentage increase in forearm volume (compared with the opposite forearm) and the pump pressure exerted by the forearm lymphatics (P_{pump}) in 16 women with breast cancer treatment-related lymphoedema. The weaker the pump, the bigger the forearm (from Modi *et al*. 2007, reproduced with permission).

lymph flow in the swollen arm, but the surge on standing still occurred.

A hypothesis

The authors noted the similarity of this concept of lymphatic failure with hypertensive cardiac failure. They proposed that a chronically increased afterload causes the lymphatic collector pump to fail after some months, resulting in the characteristically delayed onset of post-breast cancer treatment lymphoedema. But why do some women develop lymphoedema after the cancer treatment and some not? Possible explanations include constitutionally weaker lymphatic pumping in some individuals and/or a *higher* pre-morbid peripheral lymph flow, for which there is preliminary, unpublished evidence. These possibilities have implications for women recently diagnosed with breast and other forms of cancer and could be explored using recently developed, almost non-invasive nuclear medicine techniques. These techniques would also offer a way of assessing putative pharmacological therapies for lymphatic failure.

Conclusions and the future (and what to do after a bite)

The wide range of lymphatic function in health and disease was a notable feature of all the above studies. Rapid lymphatic transport (Modi *et al*. 2007) was also noted by Aas *et al*. (1985) who injected radiotracer subcutaneously in the foot of sitting subjects and detected activity in the thigh in < 1 min and in the systemic blood in 2–5 min. This makes evident the urgency of commencing first-aid measures following snake or spider bites, which are aimed at collapsing the superficial lymphatics (and veins) by compression and immobilisation, or by placing a constricting band around the limb, so as to reduce flow. Even high external pressures may fail to arrest lymphatic transport, and such pressures would in any event have to be guessed at in the field. There is also the possibility of transport of toxin from the superficial (epifascial) to the deep (subfascial) lymphatic systems, which are connected in the limbs and trunk.

The best advice is, clearly, don't get bitten!

Our understanding of the lymphatic pump, and how it is primed, is still lacking, although its importance in tissue homeostasis is recognised (Levick & McHale, 2003; Mortimer & Levick, 2004). The high prevalence of cancer treatment-related lymphoedema may serve as an impetus for future work; lymphoedema is a problem that will not go away and may even become commoner as more patients survive cancer. Curiously, breast cancer-related lymphoedema still occurs in at least 6% of patients after sentinel lymph node biopsy, in which only 1–2 lymph nodes are removed (the incidence after standard axillary treatment is perhaps 1-in-4), whereas sometimes it does not occur after complete axillary clearance surgery. A number of current clues point to a genetic predisposition to this form of lymphoedema and this may prove an exciting avenue for future exploration, with the potential to identify and treat high risk patients.

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Advances in understanding new roles for astrocytes in the modulation of neuronal activity

The nervous system consists of two classes of cells, the neurones and glia. There are three categories of glial cells in the nervous system:

- Schwann cells and oligodendrocytes, which produce myelin and wrap layers of myelin membrane around axons of the peripheral nervous system and the central nervous system (CNS) respectively, allowing fast electrical neuronal conduction;
- microglia, the immune cell type of the nervous system, responds to injury and disease by phagocytosing cellular debris and triggering inflammatory responses;
- astrocytes, which ensheath synapses and blood capillaries.

Astrocytes comprise some 50% of the volume of primate brain, and have traditionally been considered to mediate metabolic, supportive and protective functions in the CNS. It is only over the past two decades that this view has changed. In this review, we discuss recent advances in the understanding of astrocyte functions in modulation of neuronal activity.

Astrocytes have emerged as a heterogeneous and multifunctional glial population. Astrocytes have been shown to coordinate the spatial positioning of oligodendrocytes during CNS development, and attract microglia and lymphocytes during inflammatory reactions, by releasing chemokines. They also maintain tight control of local ion and pH homeostasis of the interstitial space, promote neurovascular coupling, provide metabolic substrates to neurons, and synthesize glutamine from neuronally released glutamate. In addition, they play a critical role in regulation of the synaptic level of neurotransmitters, in particular glutamate, preventing excitotoxicity. Furthermore, astrocyte functions that have recently received a lot of attention involve their roles in neurogenesis, synapse formation (Ullian *et al.* 2004), and their ability to release neuroactive substances (called gliotransmitters), which may directly modulate neuronal excitability and transmission. In this review, we will focus on the role of astrocytes in synaptic function, and more specifically, on how astrocytes sense and react to ongoing neuronal activity and rapidly modulate this activity.

Advances in our understanding of astrocytes include new observations about their structure, organization and distribution. At the morphological level, conventional electron microscopy reveals that astrocytes are closely intertwined with synapses, suggesting an astrocytic role in synapse maintenance and function. Microinjection of single astrocytes with fluorescent dyes with the use of high resolution confocal imaging illustrates their complex morphology (Fig. 1). Individual astrocytes extend major processes, each of which ramifies into highly branched and fine processes that eventually go beyond the resolution of the light microscope. The elaborate and dense processes of each astrocyte occupy distinct anatomical domains leading to minimal overlap among adjacent astrocytes (Fig. 1) and an ordered arrangement of these cells (Nedergaard *et al.* 2003).

Such an arrangement allows each astrocyte to cover a distinct territory that interfaces with microvasculature and synapses (Fig. 2*A*). Within its own domain, each astrocyte is estimated to contact 140 000 synapses, suggesting that individual astrocytes can integrate signals from multiple synapses, and similarly signal back to multiple synapses. One remarkable consequence of this structural organization is that each synapse might be under the sole influence of a single astrocyte.

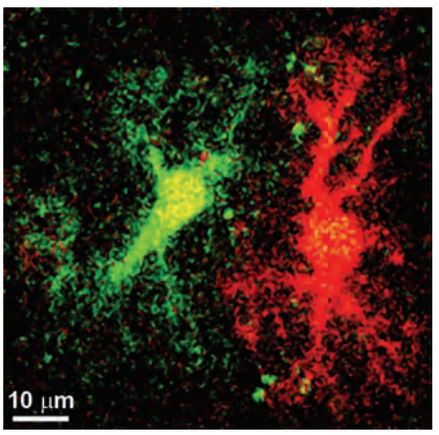


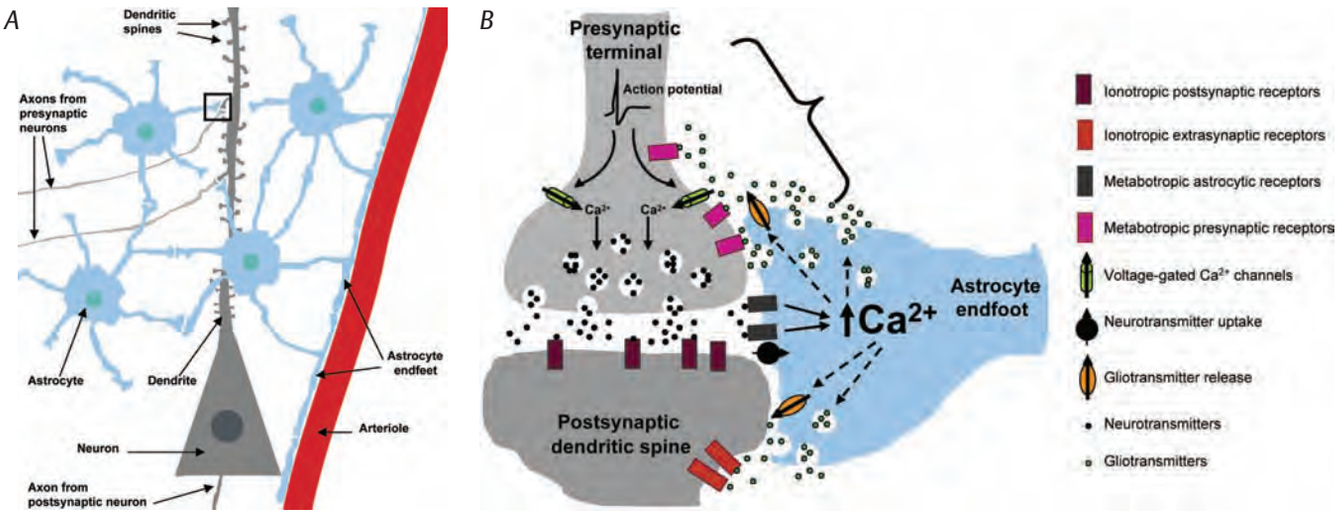
Figure 1. Astrocytes occupy distinct non-overlapping domains. Patch pipette-filled astrocytes with two different coloured fluorescent dyes (OGB-1, a green fluorescent dye; Fura-red, a red fluorescent dye) illustrating the dense arrays of processes from each cell.

Interestingly, astrocyte processes (lamellipodia and filopodia with unique structural composition and motility) make transient highly dynamic interactions with surrounding synapses in a time scale of minutes. Thus, astrocytes are plastic and have the ability to continuously redefine their shape, possibly to match the activity level of the synapse and modulate neurotransmission.

Furthermore, astrocytes form communicating networks. Many astrocytes are indeed highly metabolically and electrically coupled by gap junctions interconnecting adjacent astrocytic processes from the same cell and between other astrocytes. Gap junctions provide a direct path for fast exchange of ions (such as calcium) and small molecules, which represents one strategy for the networking of astrocyte populations (Scemes & Giaume, 2006). Gap junctional proteins, connexins, are targets of many endogenous active molecules indicating that astrocytic networks are subject to plasticity.

Other pivotal discoveries that have opened new perspectives for astrocyte functions include:

- astrocytes have many of the same neurotransmitter receptor signalling systems as neurons;
- astrocytes communicate with one



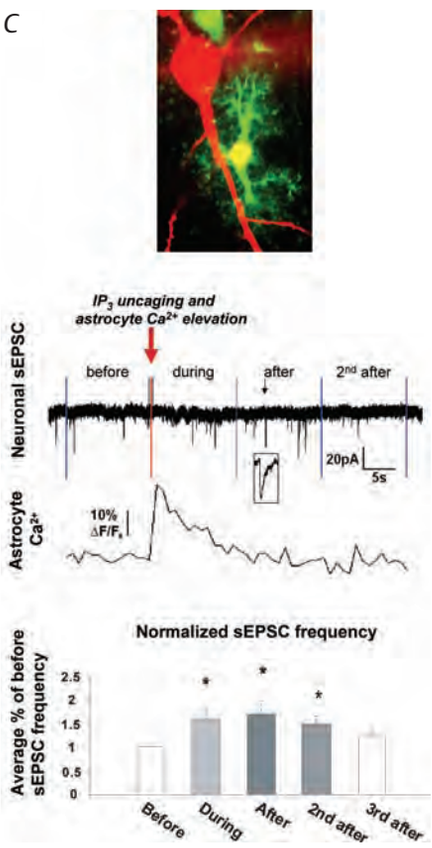


Figure 2. Bidirectional communication between astrocytes and neurons at synapses. *A*, Astrocyte endfeet closely surround CNS blood vessels, arterioles and synapses. Astrocytes have highly ramified and fine processes and occupy spatial domains that don't overlap. *B*, Enlargement of the boxed area in *A* showing that the astrocyte process enwraps tightly the pre- and post-synaptic terminals and forms the third active element at the synapse. Astrocyte processes clear neurotransmitters that accumulate following neuronal activity by plasma membrane neurotransmitter transporters. In addition, neurotransmitter release from presynaptic terminal can activate astrocytic metabotropic receptors, leading to Ca^{2+} release from internal stores and vesicular and/or non-vesicular gliotransmitter release. Gliotransmitters may under certain circumstances bind to pre- and post-synaptic metabotropic and ionotropic receptors to signal back and modulate neuronal activity. *C*, Data illustrating gliotransmitter modulation of presynaptic activity pointed with a bracket in C (modified from Fiacco & McCarthy, 2004). Evoking Ca^{2+} elevation in a hippocampal astrocyte (green cell) by uncaging IP_3, coincides with a significant increase in the frequency of spontaneous excitatory currents (sEPSC) in an adjacent neuron (red cell), due to activation of presynaptic receptors by gliotransmitters and consequent facilitation of presynaptic neurotransmitter release. Abbreviation: IP_3 : inositol-1,4,5-trisphosphate.

another and with neurons through chemical signals as opposed to action potentials;

- astrocytes have the capability to release gliotransmitters, such as glutamate, ATP, and D-serine, under specific experimental conditions to modulate neuronal excitability and transmission.

Since astrocytes are electrically non-excitable, astrocytes received little attention during the past century given that the electrical language of neurons was thought to be the only way for rapid CNS communication. Consequently, astrocytes had been presumed to be unable to initiate dialogue with neurons. However, metabotropic receptors, ion channels, and transporters allow astrocytes to receive neuronal signals. Recent advances in calcium (Ca^{2+}) imaging methods have enabled observation of astrocyte G-protein coupled receptor (GPCR)-mediated Ca^{2+} elevations in response to spillover of neurotransmitter by neuronal presynaptic terminals. Depending upon the level of neuronal activity (spanning basal activity to physiological and pathological levels of excitation) astrocyte Ca^{2+} transients can either remain restricted to microdomains of processes, or propagate as a Ca^{2+} wave intracellularly or between many astrocytes (Porter *et al.* 1996; Nett *et al*. 2002; Peters *et al*. 2003; Wang *et al.* 2006). Therefore, astrocytes might form functional networks and communicate with each other through intracellular and intercellular Ca^{2+} waves, providing a mechanism for the propagation of information over long distances. Although it has not been addressed yet, it would be interesting to check if Ca^{2+} microdomains are preferentially involved in basal physiological states when Ca^{2+} waves would be associated with a high level of neuronal activity (e.g. learning processes) and pathological states (e.g. epilepsy or brain ischemia). Properties of Ca^{2+} oscillation dynamics generated in astrocytes, including their amplitude frequency and network activity, are governed by the intrinsic properties of astrocytes and neuronal inputs. For instance, synchrony of astrocyte Ca^{2+} activity has been found to be driven by underlying networks of neurons (Aguado *et al*. 2002; Agulhon *et al*. 2007).

Interestingly, it has been reported (*in vitro* and in acute brain slices *in situ*) that Ca^{2+} rises in astrocytes may then trigger gliotransmitter release at the astrocytic processes to signal back and modulate neuronal activity locally by regulating both pre- and post-synaptic functions (Fig. 2*B*,*C*; Parri *et al*. 2001; Fiacco & McCarthy, 2004). This discovery that astrocytes have the capability to be excited and send back messages to neurones has expanded our appreciation of the complexity of CNS communication to an integrated network of both neuronal and astrocytic circuitries. However, the physiological relevance of gliotransmitter release still remains to be elucidated *in vivo*.

Although there is a large body of evidence for gliotransmitter release from astrocytes in brain slices affecting neuronal function, the mechanisms of gliotransmitter release are still controversial, since the majority of studies on release mechanisms have been carried out *in vitro*. Calcium-dependent and/or Ca^{2+}-independent effluxes through hemi-channels, P2X7 receptors, volume-regulated ion channels, and vesicular release of transmitters, have all been demonstrated (Fiacco & McCarthy, 2006). In astrocytes, Ca^{2+} signals generated by GPCRs are often encoded by different agonist concentrations eliciting Ca^{2+} elevations of variable kinetics (kinetic modulation). In addition, the Ca^{2+} signal can be conveyed by oscillations of intracellular Ca^{2+}, where agonist concentration determines the frequency of Ca^{2+} oscillations (frequency modulation). Astrocytes might encode external neuronal inputs into Ca^{2+} signals and decode them into specific types of gliotransmitter secretion.

Overall, these findings have enhanced our view of glial cell function and are among the highlights of cellular neuroscience research over the last decade. The physiological consequences of astrocyte-neuron communication on the modulation of neuronal activity and synaptic transmission suggest that astrocytes may be actively involved in information processing in the CNS *in vivo*.

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Angiotensin II and intestinal glucose uptake

An enterocyte renin-angiotensin system has been shown to be involved in AT_1 receptor mediated sodium-dependent glucose transport and thus intestinal glucose uptake. How are these findings clinically relevant to intestinal glucose transport in diabetic conditions?

The circulating renin-angiotensin system (RAS) has a major endocrine role in the regulation of arterial blood pressure, electrolyte and fluid homeostasis by acting on vascular smooth muscle, adrenal aldosterone secretion and renal electrolyte reabsorption. Dysregulation of the RAS thus leads to renal, cardiovascular and metabolic diseases. The classic RAS consists of several key elements: a liver-derived precursor angiotensinogen and two critical enzymes for the system, namely kidney-derived renin and lung-bound angiotensin-converting enzyme (ACE). The sequential actions of these two enzymes on angiotensinogen produce plasma angiotensin I and angiotensin II, respectively. Most major actions, if not all, of the RAS are mediated by the peptide angiotensin II, the physiologically active component of the system. The effects of angiotensin II are, in turn, mediated by two angiotensin II receptor subtypes, namely AT_1 receptors and AT_2 receptors (De Gasparo *et al*. 2000).

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In addition to this hormonal or circulating RAS, the past two decades has seen a recognition of functional RAS that exert autocrine, paracrine and/or intracrine control of local intercellular and intracellular functions (Paul *et al*. 2006). These functions include, to name a few, cell proliferation, apoptosis, free radical generation, hormonal secretion, local blood flow, proinflammatory and profibrogenic actions. The recent identification of a functional RAS in the pancreas and the liver has focused interest on the gastrointestinal tract as a target of RAS action (Leung, 2007; Leung *et al*. 2003). Evidence for the existence of a functional RAS in the intestine has been previously reported (Paul *et al*. 2006). However, there are no solid data for the involvement of enterocyte-derived angiotensin II in the local control of intestinal transport. Two primary functions of the intestine are the digestion of food and absorption of electrolytes and nutrients such as glucose. The absorption of glucose involves an entry-and-exit mechanism mediated by two separate protein carriers located in the brush border membrane (BBM) and basolateral membrane (BLM) of enterocytes (Wright *et al*. 1994). This established model is energized by a BBM bound ATP-dependent Na^+ pump (SGLT1) that maintains a sodium gradient favoring the entry of Na^+ with the concomitant cotransport of glucose or galactose into the enterocytes. A second carrier (GLUT2) located at BLM then facilitates the exit of glucose from the cell (Fig. 1). Notwithstanding the involvement of this secondary active transport, the regulation of SGLT1, and consequently of glucose uptake at the BBM of enterocytes is yet to be elucidated.

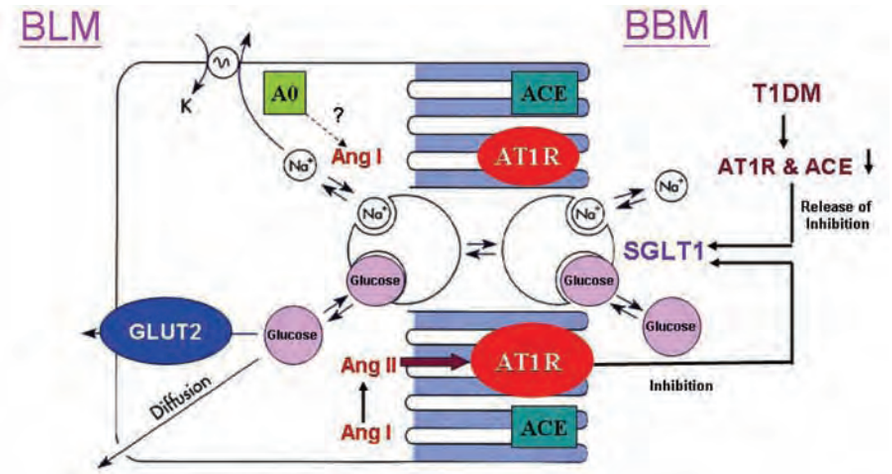

Figure 1. A schematic representation showing the proposed regulatory mechanism of an enterocyte RAS involved in intestinal glucose transport by a BBM-bound SGLT1 cotransporter. The inhibitory action of enterocyte-derived angiotensin is involved in AT_1 receptor-mediated SGLT1-dependent glucose transport at the BBM. In T1DM, the expression of AT_1 receptor and ACE at the BBM is down-regulated which in turn leads to release of inhibitory action on SGLT1-dependent glucose transport. A0=Angiotensinogen; AT1R = AT_1 receptor; ACE=Angiotensin-converting enzyme; BBM=Brush border membrane; BLM=Basolateral membrane.

We have recently found compelling evidence for the existence of an enterocyte RAS that generates angiotensin II locally and leads to a rapid inhibition of SGLT1-mediated intestinal glucose uptake (Wong *et al*. 2007). In this study, expression of key RAS components at the gene and protein levels were examined in jejunal and ileal enterocytes. Mucosal uptake of glucose by everted intestinal sleeves before and after addition of angiotensin II to the mucosal buffer was measured in the presence or absence of losartan, an AT_1 receptor antagonist. Results revealed that enterocytes express angiotensinogen, ACE, and AT_1 and AT_2 receptors; AT_1 receptor and angiotensinogen proteins were specifically localized to the BBM.

Expression of angiotensinogen (a mandatory component of a local RAS) and AT_1 and AT_2 receptors, but not ACE, was greater in the ileum than the jejunum. Addition of angiotensin II to mucosal buffer inhibited phlorizin-sensitive (SGLT1-dependent) jejunal glucose uptake in a rapid and dose-dependent manner and reduced the expression of SGLT1 at the BBM. Losartan attenuated the inhibitory action of angiotensin II on glucose uptake. Despite this inhibitory effect on glucose uptake, angiotensin II did not affect jejunal uptake of L-leucine, suggesting a specific action on glucose (Wong *et al*. 2007). Figure 1 summarizes the involvement of an enterocyte RAS which acts as an autocrine control in the rapid inhibition of SGLT1-dependent glucose uptake.

In keeping with these findings, our next question to be addressed is this: what is the clinical relevance of this enterocyte RAS in the AT_1 receptor-mediated SGLT1-dependent glucose uptake in the intestine? We hypothesized that the expression of the RAS components at the enterocyte BBM is subject to regulation by prevailing physiological and pathophysiological conditions in the jejunum and ileum.

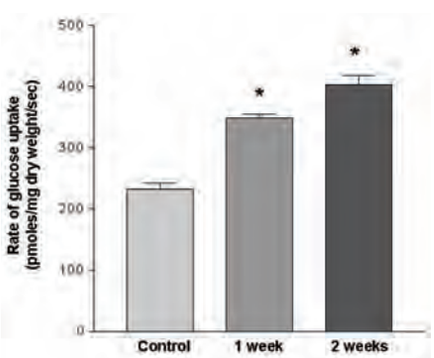

Figure 3. Effects of time-course study on jejunal glucose uptake from T1DM diabetic rats. Glucose uptake is measured by D-[^{14}C]glucose using everted intestinal sleeves. Control denotes injection of streptozotocin buffer; 1 week=one week after injection of 80 mg/kg streptozotocin; 2 week denotes two weeks after injection of 80 mg/kg streptozotocin. *=significant difference as compared with control ($p<0.05$).

We tested this hypothesis by examining the expression of enterocyte RAS components in hypoxia and in type 1 diabetes mellitus (T1DM). Preliminary results showed that the expression of RAS components was down-regulated by hypoxia and even more so by streptozotocin-induced T1DM. The expression of the AT_1 receptor and of ACE at the enterocyte BBM was significantly decreased in T1DM (Fig. 2). In addition, the intestinal uptake of D-[^{14}C] glucose was stimulated in a time-course dependent manner in the mucosa of the everted intestinal sleeve (Fig. 3). Consistent with our results, enhanced glucose uptake across kidney proximal tubule BBM due to a reduced expression of angiotensin II receptors, has been previously observed in streptozotocin-induced T1DM (Cheng *et al*. 1994). Interestingly, glucose uptake across the kidney proximal tubule BBM is strikingly similar to that seen in enterocyte BBM. Taken together, these data prompt us to speculate that down-regulation of the enterocyte RAS during T1DM may be responsible for the enhanced SGLT1-mediated glucose uptake, a finding that is closely relevant to patients with T1DM and/or T2DM (see Fig. 1).

Given this evidence for the involvement of enterocyte RAS in diabetes, it is important that we now elucidate the precise mechanisms by which enterocyte-derived angiotensin II, via mediation of the AT_1 receptor, exerts its effect on SGLT1-dependent intestinal glucose transport.

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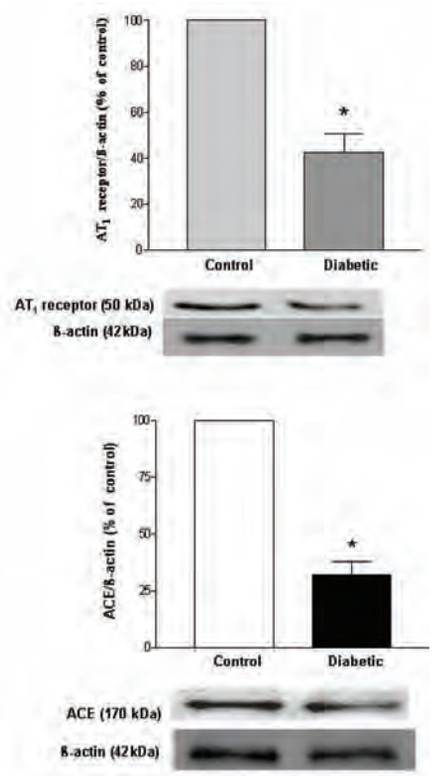

Figure 2. Western blot analysis of AT_1 receptor and ACE protein at BBM isolated from control and T1DM diabetic jejunal enterocytes of rats. *A*, Relative expression of AT_1 receptor to b-actin protein. *B*, Relative expression of ACE to β-actin protein. Control denotes 2 weeks after intravenous injection of streptozotocin buffer. Diabetic denotes 2 weeks after injection of 80 mg/kg streptozotocin.

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Improving reaction time with a bang

If a loud noise or unexpected tap on the shoulder has ever caused you to jump out of your skin, you may have wondered about the purpose of the startle reflex. Common theories include protection against injury from predators and preparation for fight or flight. Recent research shows that startle also facilitates the brain's ability to process and react to other stimuli

The startle reflex occurs in a variety of animals including mammals, insects and fish (Eaton, 1984). In humans it can be elicited by loud unexpected sound, typically >110dB. This results in widespread involuntary muscle contraction and a rise in heart rate. Commonly used indicators of startle are eye and neck muscle twitches, which occur approximately 35 and 60 ms after sound onset, respectively. These remarkably fast responses are mediated by a simple neural circuit involving the caudal pontine reticular formation in the lower brainstem, which receives direct input from various auditory nuclei. Startle may offer protection against predators by minimising bodily damage and preparing the body for fight or flight (Fig. 1). However, the true purpose of the human startle reflex, if any, remains a matter of speculation.

In addition to its direct effects, startle can have secondary effects upon ongoing behaviour. One might assume these would only be obstructive, and this is certainly true for actions which demand a high level of precision. However, research over the past decade shows that the acoustic startle response can actually enhance performance on some basic tasks. When an experimental subject is asked to flex a wrist as quickly as possible following a flash of light, reaction time (RT) is almost halved when the visual stimulus is accompanied by a startling sound. In this 'simple' reaction task (SRT), the required movement is known in advance and so it can be prepared and stored. Startle causes this stored response to be released earlier than normal (Valls-Sole *et al*. 1999). This is not merely due to the startle response being incorrectly interpreted as the intended movement. Close inspection of muscle activity reveals the purposeful characteristics of an intended movement, not a random burst (Fig. 2).

Raymond Reynolds (left) and Brian Day

What about more complex movement? In a 'choice' reaction task (CRT), the required movement depends on the nature of the stimulus. For example, this might involve pressing a button with the right or left hand, after seeing a square or triangle, respectively. In this case the required movement is not known in advance and so cannot be prepared. Some degree of visual processing is required, before the appropriate movement can be selected. Previous research suggests that startle interferes with CRT. However, two papers in a recent edition of *The Journal of Physiology* show that RT can be improved in certain types of CRT. Oude Nijhuis *et al*. (2007) applied acoustic startle when subjects rotated their head to the left or right, after seeing a visual stimulus. Startle reduced reaction time by 56 ms. Reynolds & Day (2007) looked at visually guided step adjustments using a target jump paradigm. These reactions are very fast even without startle (<125 ms), but startling sound caused them to be reduced further by ~20ms (Fig. 3). In both of these tasks, the startle response is not simply causing the early release of a prepared response, since the required movement is not known until the visual stimulus is presented. Instead, it reduces the time taken to process a visual stimulus and select the appropriate response.

What is the mechanism by which startling sound improves reaction time? The answer may lie in the brain areas responsible for generating the

Figure 1. Startled armadillo. The armadillo leaps in response to the photographers flash. This response may help it escape predators. By Bianca Lavies © 1982 National Geographic Society.

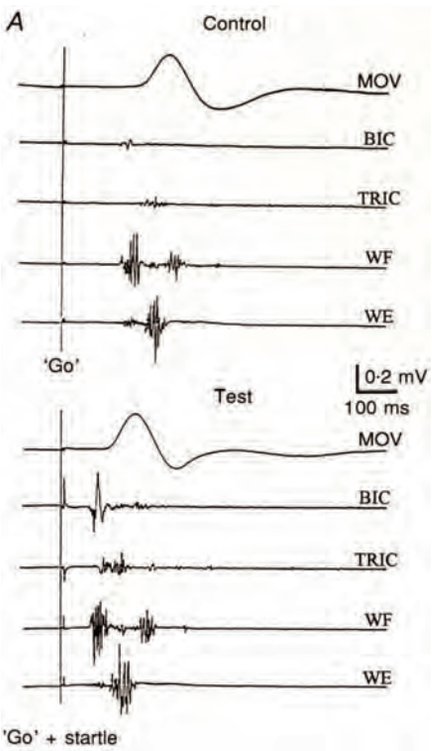

Figure 2. Effect of acoustic startle on simple reaction time. Movement and muscle activity during a wrist flexion task. During control trials without sound the characteristic tri-phasic muscle pattern of ballistic movement can be seen in the wrist flexors and extensors (WF & WE). When a loud sound is presented at the same time as the visual stimulus, the same pattern occurs earlier in time (from Valls-Sole *et al*. 1999).

behaviour. For SRT tasks, it has been suggested that movements can be prepared and stored at a sub-cortical level. The startle reflex, generated in the lower brainstem, interacts with this stored motor programme causing its early release. For CRT tasks startle may also exert its effects at a sub-cortical level, but in this case to improve visuomotor processing. So it may be the case that only basic, reflex-like behaviour which operates through sub-cortical circuitry can benefit from startle. Visually guided limb adjustment and head orientation both fall under this category (Walton *et al*. 2007; Day & Brown, 2001). Conversely, more complex tasks involving arbitrary visuomotor associations depend more upon cerebral processing, and so may only be disrupted by startle. Further behavioural data will hopefully resolve this issue.

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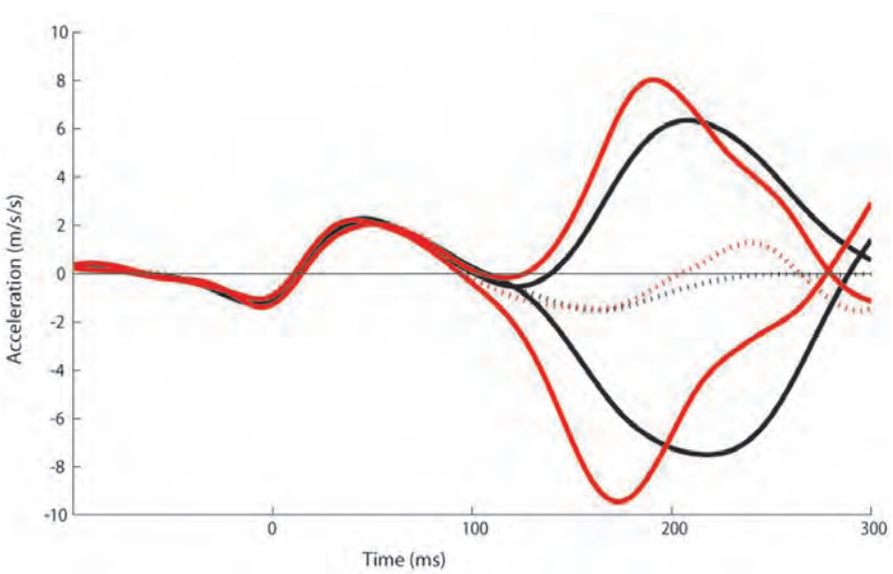

Figure 3. Effect of startle on rapid adjustment. Traces show lateral acceleration of the right foot in response to a moving target (+ve is rightward movement). Red traces show the effect of startling sound. Dash traces show control trials with no target jump. When loud sound and target jump are given simultaneously, reaction time is faster (from Reynolds & Day, 2007).

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BSF open access survey

A survey commissioned by the Biosciences Federation has found that increases in open access publishing could have a detrimental effect on funding streams to UK universities. The Biosciences Federation commissioned a survey of its member learned societies and individual society members to ascertain the effect that open access might have on the publishing community and the funding structure of the learned societies themselves. The survey examined three areas – financial flow between the UK research community and learned societies, societies' publishing policies and experience with open access and authors' own experience and opinions on open access and self-archiving.

The survey also found that, where open access publication is compulsory, researchers still prefer to use the final version published in peer-reviewed journals rather than institutional or subject repositories.

Ian McGrath, Chair of The Society's Executive Committee, and Mike Collis, Chief Executive of The Society, are on the BSF journals committee and were involved in management of the project, and in the final structure and text of the report.

The full report is available at http://www.bsf.ac.uk

The embryo and a lifetime of staying healthy

Can the risk of adult-onset disease be influenced more by your development as an embryo than your lifestyle as an adult?

The development of adult-onset diseases, such as type II diabetes, obesity and cardiovascular disease, has traditionally been associated with adult behaviour such as a sedentary lifestyle, poor diet and smoking.

However, over recent years a growing body of evidence from both human and animal models has challenged this concept and reveals that environmental conditions experienced during critical windows of gestation can have an even greater influence on adult health (Barker & Bagby, 2005; Hanson & Gluckman, 2008). Indeed, research from human, rodent and livestock studies has identified the earliest stages of development, prior to embryo implantation, to be particularly sensitive to changes in their immediate environment either *in vitro* (e.g. culture conditions) or *in vivo* (e.g. maternal diet) with long-term consequences into adult life (Watkins *et al*. 2007, 2008a, b, c).

Mammalian preimplantation development encompasses the period between fertilisation of the egg and implantation into the uterine wall (approximately 4 days in the mouse and 6 in the human; Fig. 1). *In vivo*, the preimplantation embryo is largely dependent upon the maternal reproductive tract environment to provide the necessary metabolites and growth factors to sustain and progress development. This dependency can be easily demonstrated by removing the embryo from the reproductive tract and culturing it *in vitro*. This commonly results in a slower rate of development and a reduced number of embryonic cells. However, the effects of embryo culture are not solely confined to the period of preimplantation development but can persist into later pregnancy and the postnatal period affecting growth, physiology and health of the offspring. One of the most dramatic examples of how embryo culture conditions can impact upon long-term development is the phenomenon of 'large offspring syndrome' (LOS). LOS is observed following the culture of sheep and cattle embryos, usually in the presence of serum. As the name suggests, LOS animals are born significantly heavier with abnormal sizes of internal organs, altered patterns of gene expression and increased rates of perinatal death (Sinclair *et al*. 2000). In mice, embryo culture has been associated with altered gene expression and regulation, the development of postnatal hypertension, altered renin-angiotensin system (RAS) homeostasis, and abnormal behaviour and memory characteristics (Fig. 2; Watkins *et al*. 2007, 2008a). These findings from animal studies pose questions about the long-term health of children conceived via assisted reproductive techniques (ART). In humans, the impact of ART on long-term health is, at present, difficult to gauge. Whilst children conceived through ART are more likely to be born prematurely and with a low birth weight (<2500g), this has been attributed to the increased incidence of ART-induced multiple pregnancies and inherent defects in the quality of parental sperm/eggs (Ludwig *et al*. 2006). It is therefore essential for follow up studies to be continued to assess the safety of ART.

Tom Fleming (left) and Adam Watkins.

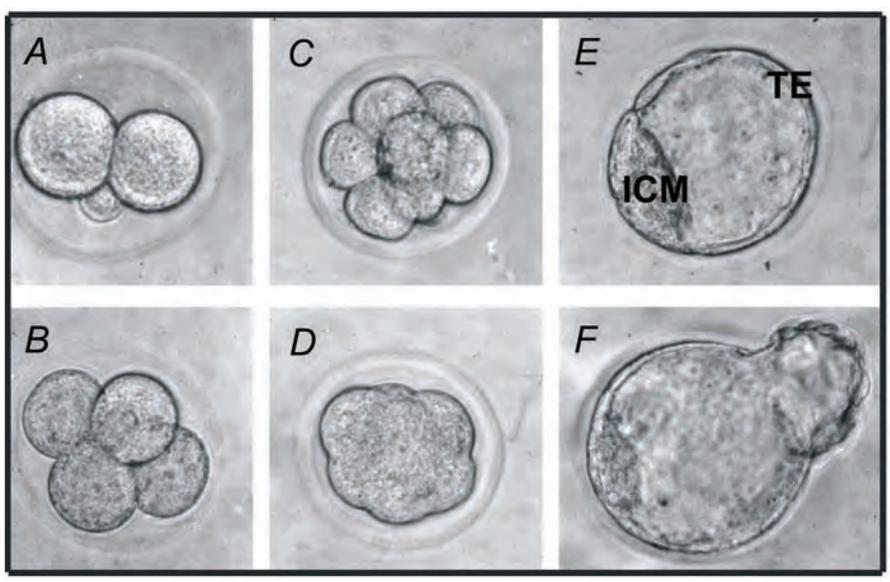

Figure 1. Photomicrographs showing the different stages of mouse preimplantation embryo development. After fertilisation of the oocyte, the zygote cleaves to form the 2-cell embryo (*A*), with subsequent rounds of cleavage yielding the 4-cell (*B*) and 8-cell (*C*) stage embryo. At the 8-cell stage, the embryo undergoes a process of compaction initiated through the expression of cell adhesion molecules, to form the morula (*D*). This allows for the generation of two distinct cell lineages, the outer epithelial-like trophectodem (TE) the pluripotent inner cell mass (ICM) evident at the blastocyst stage (*E*). Just prior to implantation, the embryo hatches through the outer glycoprotein coat, the zona pellucida (*F*).

Manipulating maternal diet has allowed us to determine the long-term consequences of altering the environment of the preimplantation embryo *in vivo*. When we provided a low protein diet (LPD) to mothers exclusively during the preimplantation period (Emb-LPD) the female offspring were born significantly heavier than control offspring. These

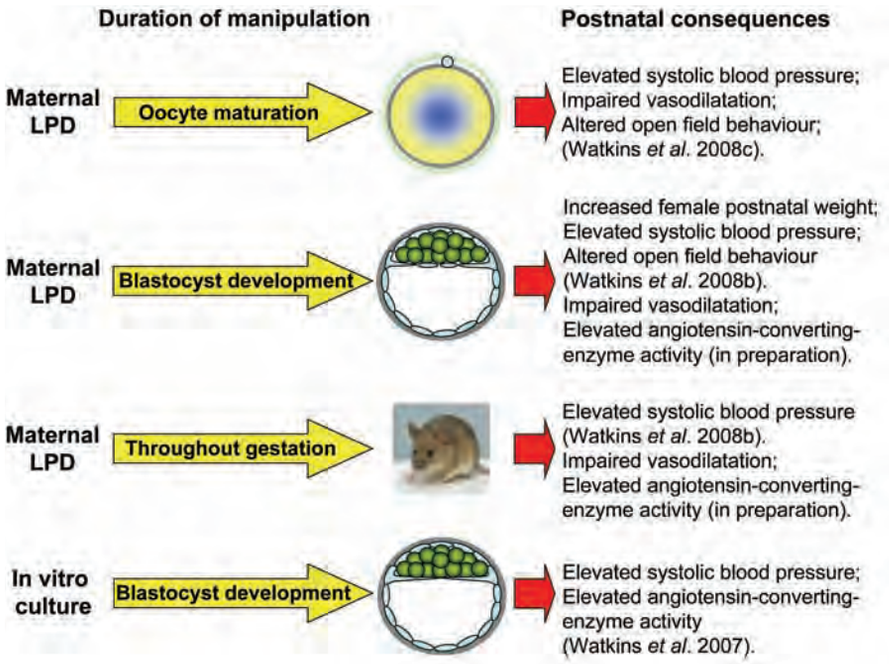

Figure 2. Diagram showing the long-term postnatal consequences of manipulating the environment of the mouse preimplantation embryo either in vivo or in vitro. Maternal LPD given exclusively during oocyte maturation, preimplantation development or throughout gestation results in altered postnatal growth, hypertension, and impaired vasodilatation of isolated mesenteric arteries. Embryo culture, and subsequent transfer, results in hypertension in the resultant offspring.

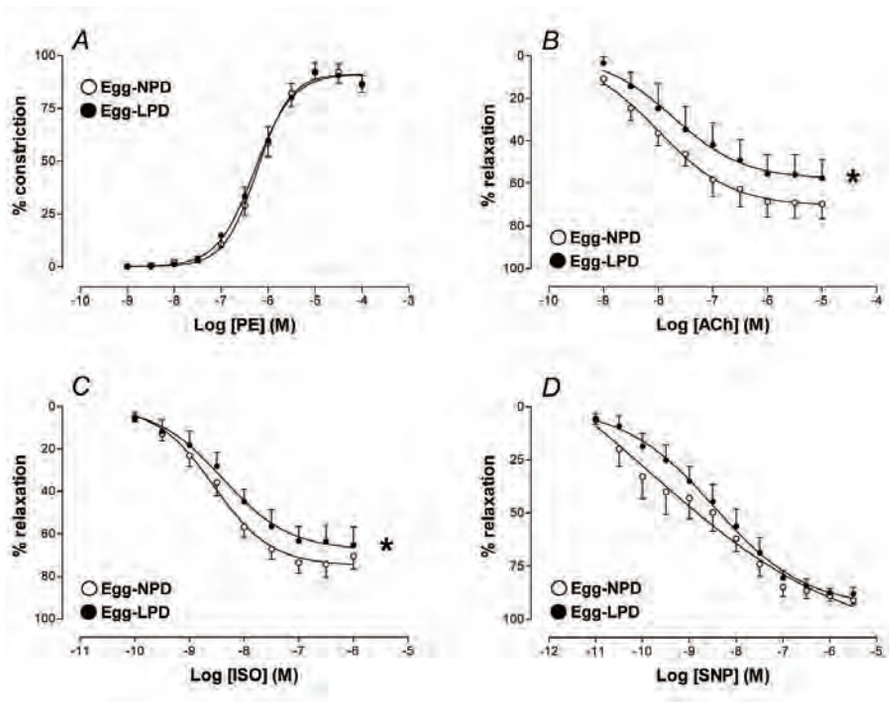

Figure 3. Maternal LPD during oocyte maturation reduces the vasoreactivity of isolated male offspring mesenteric arteries at 22 weeks compared to NPD (normal protein diet treatment). Cumulative additions of (*A*) phenylephrine (PE) and, after pre-constriction with PE of the vasodilators (*B*) acetylcholine (ACh), (*C*) isoprenaline (ISO) and (*D*) sodium nitroprusside (SNP). No difference is observed in responsiveness to PE or SNP between treatments, however, Egg-LPD arteries display attenuated responses to ACh and ISO when compared to Egg-NPD arteries. Values are mean ± SEM; n = 7 males, each from different litters, from each treatment group; $^{*}P < 0.015$. Figure taken from Watkins *et al*. (2008c).

females remained heavier for up to 6 months of age and displayed abnormal locomotor activity in the open field test (Fig.2; Watkins *et al*. 2008b). Moreover, both male and female offspring from the maternal LPD treatment became hypertensive throughout adult life (Watkins, 2008b). Similarly, we found that in the rat, maternal LPD during the same period of development reduced the number of cells present within blastocysts and altered the pattern of gene expression in the blastocyst and later conceptus stages, leading to gender-specific changes in postnatal growth and systolic blood pressure (Kwong *et al*. 2000, 2006, 2007).

In sheep, maternal undernutrition prior to conception, or the feeding of a high protein diet, reduces the viability of oocytes and embryos, alters the patterns of fetal and postnatal growth and fetal endocrinology status, induces hypertension and increases the responsiveness of arteries to vaso-constrictive compounds (Cleal *et al*. 2007; Sinclair *et al*. 2007; Watkins *et al*. 2008a). Recently, we observed that maternal LPD exclusively during mouse oocyte maturation (3.5 days prior to mating; Egg-LPD) resulted in offspring developing hypertension and altered patterns of open field behaviour (Fig.2; Watkins *et al*. 2008c). This hypertensive state was associated with significant impairment in mesenteric artery vasodilatation in response to the endothelial-dependent and independent vasodilators acetylcholine (ACh) and isoprenaline (ISO) respectively when compared to controls (Fig. 3).

The global prevalence of diseases such as obesity, cardiovascular disease and diabetes is increasing at a dramatic rate and is no longer confined to developed countries. The studies outlined above demonstrate a clear link between egg and embryo environment and development and the onset of these adult diseases in animal models. Further studies are urgently required to determine the molecular, biochemical and epigenetic mechanisms underlying

such associations, and to the extent to which these relationships may exist in humans.

Acknowledgements
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Elephant steaks?

Peter Daniel was elected a Member of The Physiological Society in 1949, and an Honorary Member in 1981. It is 10 years since he died but his contributions to The Society are not forgotten by those who benefited from them.

He is remembered too in another context. During his time as Professor of Neuropathology at the Institute of Psychiatry at the Maudsley Hospital he would collect material from animals that had died at London Zoo; these included an elephant's skull and brain. Peter, wearing a white lab coat, showed them to the Queen Mother when she came to open a new building at the Hospital. The local paper captioned the picture of this event as *The Queen Mother discussing the patients' food with the head cook*.

Ann Silver
Cambridge, UK

Eating junk while pregnant can harm your baby

Research published in *The Journal of Physiology* suggests that poor diet may cause long-lasting, irreversible damage in offspring such as heart disease and diabetes.

Stéphanie Bayol and Neil Stickland at the Royal Veterinary College, London fed female rats a 'junk food' diet of crisps, cheese, muffins and other processed foods throughout pregnancy and lactation.

The offspring, who were overweight at birth, were born with a taste for junk food themselves. But even when fed a healthy diet, the junk food babies had a host of medical problems that lasted beyond adolescence into adulthood.

The rats had raised cholesterol and triglyceride levels – both associated with heart disease. Insulin and glucose in the blood were also unusually high, known to be a cause of type-2 diabetes, and the rats remained significantly podgier than normal with extra fat around the kidneys, another diabetes risk-factor.

The female offspring were particularly badly affected, expressing high levels of glucose and the appetite-promoting hormone leptin, making them very prone to obesity.

'It seems that a mother's diet whilst pregnant and breastfeeding is very important for the long term health of her child', says Stéphanie Bayol. 'This does not mean that obesity and poor health is inevitable and it is important that we take care of ourselves and live a healthy lifestyle. But it does mean that mothers must eat responsibly whilst pregnant.'

But will these results translate to humans? Very probably, says Neil Stickland. 'Humans share a number of fundamental biological systems with rats, so there is good reason to assume the effects we see in rats may be repeated in humans. Our research certainly tallies with epidemiological studies linking children's weight to that of their parents.'

Bayol SA, Simbi BH, Bertrand JA & Stickland NC (2008). Offspring from mothers fed a 'junk food' diet in pregnancy and lactation exhibit exacerbated adiposity that is more pronounced in femals. *J Physiol* **586**, 3219–3230.

Airway protection is a vital function that supersedes volitional tasks

Airway protective reflexes are not suppressed during volitional tasks for voice and breathing and appear to be an exception to reflex suppression during volitional tasks

To produce voice for speech and song, the muscles within the vocal folds (the thyroarytenoid muscles) must contract to bring the vocal folds together in the middle of the airway. When expiratory air flow from the lungs provides adequate air pressure to induce vibration, an acoustic excitation occurs in the tract to produce the human voice. The muscle adjustments must be rapid in order to precisely control voice onset and offset for distinguishing between voiced (e.g. /b/) and voiceless consonants (/p/) during ongoing speech. In addition, the tension within the folds and the subglottal pressure are modulated to produce changes in voice pitch and loudness for both speech and song.

The laryngeal muscles are also important for airway protection; they close the vocal folds to prevent the entry of food, liquid or particles past the folds into the lungs. The laryngeal adductor response (LAR) is a brain stem reflex that produces vocal fold closure and is triggered when the mucosa covering the vocal folds and/or the laryngeal vestibule are stimulated. The superior laryngeal nerve contains the afferents whose endings innervate the laryngeal mucosa. If stimulation is intense and prolonged, a life threatening uncontrolled closure of the airway (laryngospasm) can occur.

Victor Henriquez (left) and Christy Ludlow.

Cortical control is involved in both the fine motor control of the voice and volitional limb movements. During purposeful arm movements, sensory input that normally produces muscle reflexes is suppressed. This suppression prevents reflex responses from interrupting or perturbing cortically controlled precise rapid arm movements (Adamovich *et al.* 1997). In non-human primates, reflex suppression during volitional limb movements appears to be caused by descending cortical signals that inhibit incoming afferent signals to the spinal reflex circuits (Seki *et al.* 2003). Similar suppression of afferent inputs from the superior laryngeal nerve to the brainstem during speech or singing, however, might be detrimental to airway protection and allow entry of saliva or foreign substances into the lungs during these activities. We studied how these two laryngeal functions — fine motor control during voice and reflexive airway protection —inter-relate.

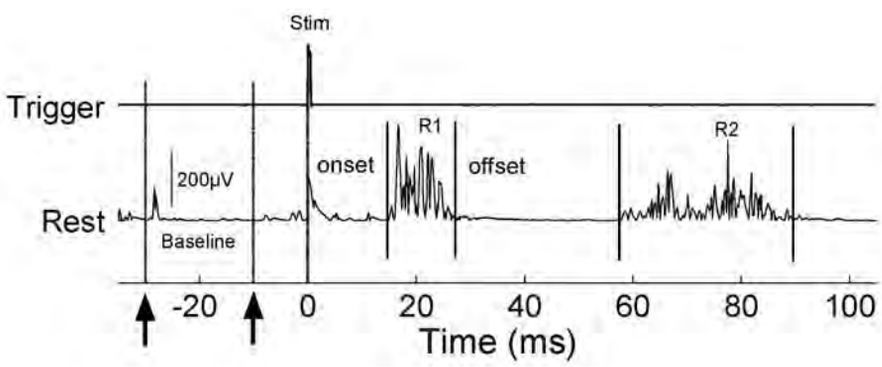

Figure 1. Typical Laryngeal Adductor Response (LAR): R1 and R2 responses in the right thyroarytenoid muscle to single electrical stimulation of the superior laryngeal nerve recorded during rest. The rectified response for the task was aligned to stimulus onset (0ms) when the Transistor to Transistor Logic (TTL) trigger was presented in the top trace. Baseline activity (Baseline, dotted lines at arrows) was measured by averaging the EMG signal over a 20ms period prior to stimulus onset (Stim). The R1 and R2 onsets and offsets (solid lines) were marked for each trial.

The LAR will produce vocal fold closure when elicited either by presenting an air puff to the mucosa overlying the vocal folds (Bhabu *et al.* 2003) or by stimulation of the internal branch of the superior laryngeal nerve (Ludlow *et al.* 1992). The superior laryngeal nerve in the neck can be stimulated using hooked wire electrodes inserted along the course of the nerve deep in the neck. This will produce a LAR with two components, a short latency ipsilateral R1 and a longer latency bilateral R2. These responses can be recorded during voice and breathing from thin wires inserted into the thyroarytenoid muscles (Fig. 1).

We compared the frequency of occurrence and the amplitude of the LAR in response to electrical stimulation of the internal branch of the superior laryngeal nerve during voice production and breathing tasks: a prolonged vowel, humming, breath holding at the larynx, or breathing in. When the LAR during these tasks was compared with quiet breathing no change occurred in the R1 response frequency or amplitude in any of the tasks. We also examined how the LAR affected muscle activity during task performance. During vowel production, breath holding, and prolonged inspiration muscle tone is increased or decreased in the thyroarytenoid muscle as the vocal folds are held closed or open respectively. We examined whether the LAR summated with the increased muscle activity (Fig. 2*B*), was reduced or masked by the muscle activity (Fig. 2*C*) or momentarily interrupted (suppressed) muscle activity (Fig. 2*D*). Because there was

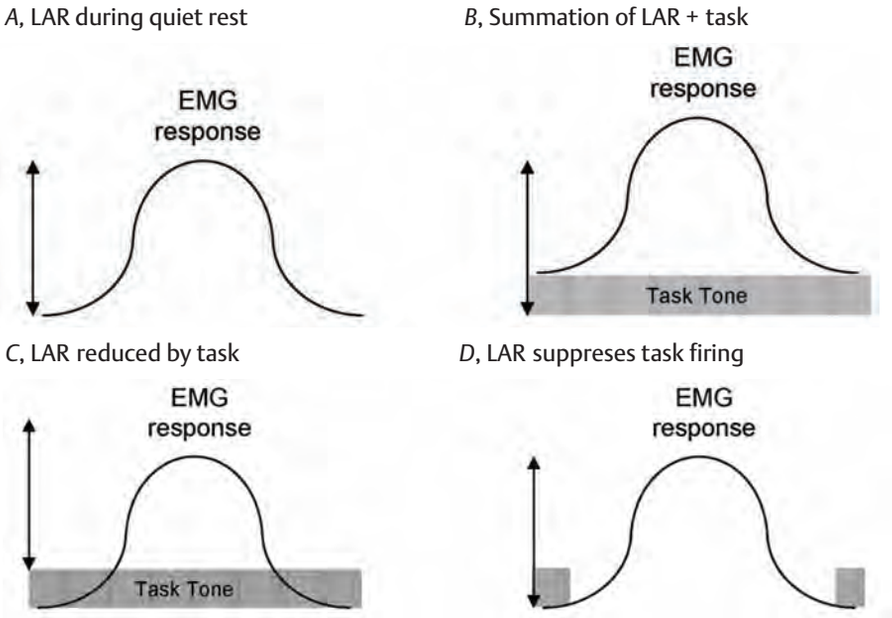

Figure 2. Hypothetical results: schematic representation of a typical rectified EMG response envelope for either an R1 or an R2 response: These represent different hypotheses regarding modulation of the laryngeal adductor response (LAR) elicited by electrical stimulation of the superior laryngeal nerve during voice or respiratory tasks. During quiet rest, the amplitude of the LAR is represented as the area under the curve (A). With summation, the LAR may add to the increased muscle tone for performance of the task (Task Tone, B). Alternatively, descending cortico-bulbar drive to the motor neuron pool may reduce the motor neuron firing for the LAR reducing the measured area under the curve (C). If the LAR amplitude is unchanged from quiet then there may be momentary suppression of the task tone during the occurrence of the LAR (D).

no difference between the size of the LAR at rest and during volitional tasks, the LAR suppressed the muscle activity for the task momentarily when it occurred (Henriquez *et al.* 2007).

The longer latency response, R2, was reduced in frequency of occurrence by about 50% during both humming and effort closure and, to a lesser degree, during inspiration and vowel production. Likely cortical modulation was able to suppress this longer pathway. On the other hand, it did not modulate the more direct R1 pathway from the afferent terminations in the interstitial subnucleus of the nucleus tractus solitarius, via the lateral tegmental field to the laryngeal motor neurons in the nucleus ambiguus (Ambalavanar *et al.* 2004).

Previously, our group has found that volitional swallowing can transiently suppress the LAR in normal subjects (Barkmeier *et al.* 2000). Swallowing, however, must also incorporate parts of the protective airway reflex system as vocal fold closure occurs in the middle of the pharyngeal phase to prevent aspiration of food or liquids into the lungs. The LAR, therefore, is commensurate with airway protection during swallowing and may be suppressed by the brainstem central pattern generator when engaged during volitional swallowing.

The tenacity of airway protection over volitional laryngeal control for voice and respiration is illustrative of its importance. From a functional perspective, volitional laryngeal tasks for voice sustain the critical human activity of communication, but these are not essential for survival. The importance of preserving airway protection at the level of the brain stem overrides muscle activity for voice, breath holding and inspiration. Control of the laryngeal muscles during volitional tasks is therefore an exception to the general pattern of reflex suppression during volitional movement.

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New publishing contract signed with Wiley-Blackwell

The Society has signed a new contract with Wiley-Blackwell to publish *The Journal of Physiology* and *Experimental Physiology*. An important feature of this contract is the guarantee of a minimum income to The Society. This guaranteed publishing income, supplemented by membership fees, income from meetings and investments, gives The Society a secure financial basis for its charitable activities and enables long term planning.

Sport genetics: physical performance potential is dependent on genome

Gene association and case-control studies have linked certain genetic variants with physiological performance traits in humans. Our personal athletic *potential* depends on our genotype, while how close we get to *achieving* our personal potential depends on environmental factors (training, diet, lifestyle, etc.). In fact, the *complexity* of the human genome limits our personal athletic potential more than was appreciated previously

In exercise physiology, we have traditionally been interested in topics such as training methods and diet and how these alter physiological function. However, twin and family studies have shown that these environmental factors probably only determine around 50% of the variability in key aspects of exercise physiology like muscle strength, fibre type and maximal oxygen uptake (Spurway & Wackerhage, 2006). For the other 50% of the variability in these phenotypes, we need to consider hereditary, genetic factors (Fig. 1). The 50% value is a generalisation because it depends on which exercise-related phenotype is being considered, but it is remarkable how often the extent of genetic influence seems to be around the 50% mark. Building upon the mass of information revealed by the Human Genome Project and associated advances in the ease and sophistication of molecular genetic techniques, advances are now being made in our understanding of the genetic factors that influence physical capability.

Some genes have been associated with physical capability in the untrained state. For example, a polymorphism of the CNTF gene

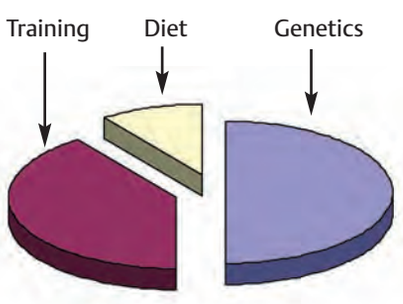

Figure 1. Simple model estimating key factors influencing exercise capacity and their magnitude. Other lifestyle factors probably also play a role.

Alun Williams (left) and Jonathan Folland.

(ciliary neurotrophic factor; a protein related to differentiation and survival of motor neurones, and intracellular signalling pathways in muscle) was associated with muscle mass and strength in a cross-sectional study of a non-athletic population (Roth *et al.* 2001).

There are also gene-environment interactions that at least partially explain the differences between individuals in their response to training. For example, a variant of the ACE gene (angiotensin I converting enzyme 1) has been associated with a reduced oxygen requirement for exercise following several weeks of training (Williams *et al.* 2000) and with endurance performance in hypoxia in several studies. Other genetic polymorphisms have been associated directly with elite athlete status (rather than a distinct physiological phenotype *per se*), conferring an advantage either independent of physical training or via a gene-environment interaction. For example, a polymorphism of the ACTN3 gene (actinin alpha 3; a protein found in the Z line of human muscle fibres that may play structural and signalling roles) has been associated with high achievement in power sports (Yang *et al.* 2003) and muscle fibre type composition (Vincent *et al.* 2007). Many of us will have memories of perhaps being at school and noticing that classmates seem extraordinarily 'naturally' talented at athletic events. Perhaps a few readers will have memories of actually being those physically talented individuals – that is, more 'naturally' talented than their peers. It is likely that genetic variation at loci such as CNTF, ACE or ACTN3 played a role in producing those differences.

A combinatory approach

However, each genetic polymorphism only seems to account for a few per cent (at best) of the inter-individual variation in physical capability. A rare attempt to recognise the contribution of two related polymorphisms in a single study (FST and ACVR2B; follistatin and activin A receptor type IIB, a myostatin antagonist and the primary myostatin receptor gene, respectively) illustrates the direction of future research, although statistical powering issues prevented an analysis of both polymorphisms simultaneously (Walsh *et al.* 2007). A true attempt to recognise the combined contribution of two polymorphisms (ACE and BDKRB2 [bradykinin receptor B2]; both related to kinin metabolism and hence nitric oxide production) did indeed better discriminate between individuals' oxygen requirement during exercise than when considering just one gene in isolation (Williams *et al.* 2004).

Accordingly, to gain a more complete picture of the genetic factors that account for around 50% of the variability in physical capability, a model is required that recognises the contribution of each gene, gene-environment and gene-gene interaction in making a complete exercising athlete.
In a recent analysis we produced the first genetic algorithm for human endurance performance. Using literature searching and specific inclusion criteria, 23 genetic

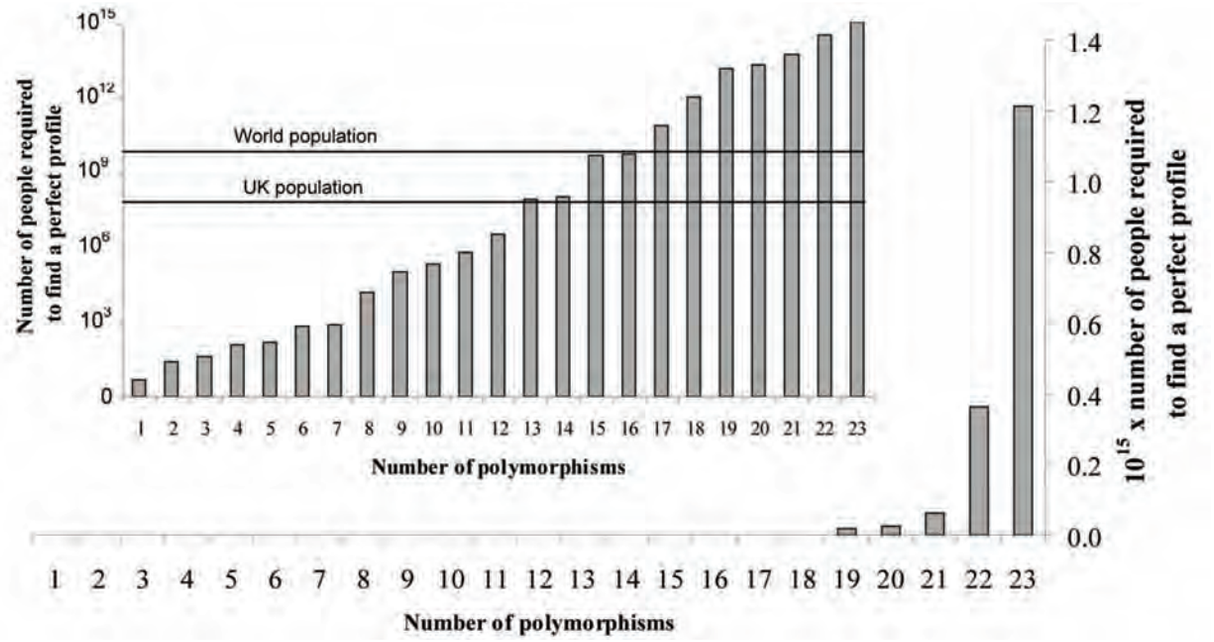

Figure 2. Large graph shows the population size required to expect one individual to have a 'perfect' genetic profile of up to 23 polymorphisms. For < 19 polymorphisms, the bars exist (number of people < 1.7×10^{13}) but are too small to be visible. Therefore, the inset graph shows the same data on a log scale, with UK and world population levels identified. The population sizes required to expect one individual to have all 23 optimal genotypes clearly exceed UK and even world levels.

polymorphisms were identified and included in the algorithm (Williams & Folland, 2008). Some of the polymorphisms included were associated with endurance characteristics independent of training, others with the magnitude of the training response and still others were identified via case-control studies between elite athletes and healthy controls. The polymorphisms were typically located within genes coding for muscle structural proteins, enzymes involved in energy metabolism and mitochondrial function (including some of those genes already mentioned in the current article). By definition, the algorithm takes into account the influence of many genes simultaneously.

Genetic 'perfection' for sport is highly improbable

Based on the typical frequencies of the 23 polymorphisms in the wider population and using the genetic algorithm, we calculated the probability of any given individual possessing all 23 'preferable' genotypes is just 8.2×10^{-14} %, an enormous odds ratio of 1 in 1,212 trillion. This equates to just a 1 in 200,000 chance that a single individual exists in the world (~6.5 billion population) possessing the 'preferable' form of all 23 polymorphisms. Even allowing a couple of 'disadvantageous' genotypes within the 23, the data suggest just a 10% chance that an individual exists anywhere with 21 of the 23 'preferable' genotypes. Fig. 2 shows how these data translate into population sizes. In essence, the complexity of the human genome combined with interindividual genetic variability, appear to limit our physical performance potential due to the improbability of possessing the 'preferable' version of each important gene. This may explain the fastest possible time predicted for a marathon of 1:57:58 (Joyner, 1991) has not yet been achieved. Presumably, we are still waiting for an individual to have both a suitable upbringing (opportunity and inclination for sport) and DNA containing the suitable versions of the important genes. We will have to wait an extremely long time for such an individual to be born – at least, in the absence of deliberate genetic manipulation, which is quite another story.

There are several limitations to the algorithm. First, it is based on data from Caucasians only, because this ethnic group alone has been studied sufficiently. Second, research into the genetics of physical performance is still in its infancy and further replication of published associations will increase confidence. Third, further gene polymorphisms will inevitably be associated with endurance parameters as our understanding improves. Consequently, the genetic algorithm proposed can be thought of as 'Endurance Algorithm version 1.0'. It will certainly need upgrading as knowledge develops. Perhaps it will be version 4.3 or later before the algorithm includes sufficient statistically important information to become practically useful either in identifying physical prowess and talent for sport or low physical capacity and propensity for ill-health.

The algorithm provides a 'total genotype score' (TGS) between 0-100 that indicates an individual's genetic predisposition for endurance performance, where a higher score is better for endurance. We calculate that 99% of people have a TGS within the range 37–65. Perhaps individuals with a TGS >65 or so could be identified as potential future elite athletes and selected for intensive training. Similarly,

individuals could be identified for whom low physical capacity may contribute to poor health. Individuals could be identified for whom exercise for health is likely to prove particularly effective, while others could be identified for whom drugs to prevent/treat a particular condition may be warranted in addition to exercise. This is how 'personalised medicine' may interface with sport and exercise genetics in the future.

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Society Member Dame Nancy Rothwell (University of Manchester) with journalist and broadcaster Vivienne Parry, at the cosy venue of the café in The Dana Centre in London on 30 April 2008. They chatted about Nancy's research on brain injury and stroke, the role of luck and challenges in science, engaging with the public on animal research and some of the particular career issues faced by women in science. The event ended with a lively debate with the general public.

Distinguishing acute and chronic effects of placental dysfunction on maternal blood pressure

Pregnancy is a state of adaptive hypotension. The mechanism of this hypotension is still poorly understood but consists of a dramatic endocrinological reaction to placental vasodilators and low grade immune reactive responses.

In pregnancy, the links between cardiac output, systemic vascular resistance and blood pressure were finally determined by physiological studies performed in primates (Phippard *et al*. 1986) and later confirmed in humans (Clapp *et al*.1988). The prior view was that the decrease in blood pressure was due to changes in cardiac status. The primary change is in fact a decrease in vascular resistance (pulmonary and systemic) which leads to a compensatory renin aldosterone angiotensin system (RAAS) activation to restore blood volume and mitigate against any further fall in maternal blood pressure. Resistance to normal pressor responses is also a hallmark of pregnancy (Gant, 1973) and identifies the profound nature of the vasodilatory response. Recent findings of angiotensin 1/bradykinin receptor role in this resistance are intriguing (Granger, 2006).

Pre-eclampsia is one of the commonest medical complications of pregnancy and accounts for 75000 maternal deaths per year and 300 000 perinatal deaths. The hallmark of this disease is hypertension and the accompanying cerebral, hepatic and renal complications demonstrate a widespread endothelial injury. This is best typified by endothelial swelling and disruption in the renal glomerulus which presents clinically as proteinuria. The increase in maternal blood pressure is due to an increase in systemic vascular resistance which is profound and demonstrates a reversal of the changes outlined above, i.e. a loss of pressor resistance, a decline in RAAS activation and a decline in cardiac output. The changes in cardiac function are also due to endocardial dysfunction as part of this widespread abnormality (Simmons, 1999), and happen surprisingly quickly.

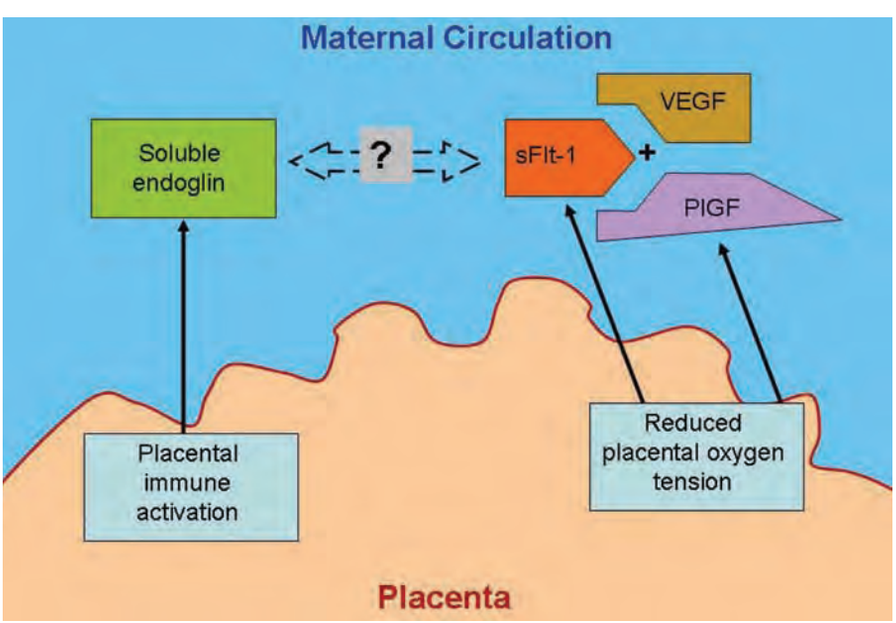

Figure 1. The reaction of placental cells, trophoblast cells, to the immune activation at the feto-maternal interface and to low local oxygen tension include the production of circulating factors endoglin and VEGF. The balance is normally towards that of vasodilation, but in preeclampsia the excessive production of soluble receptor sFlt-1 overwhelms the capacity of VEGF to vasodilate and hypertension results.

Angela Makris (left) and Annemarie Hennessy.

A great discovery with regard to preeclampsia over the last 4 years has been the identification of endothelial cell 'toxins' which are biologically plausible as mediators of endothelial dysfunction (Fig. 1). These include angiogenic factor fms-like-tyrosine kinase-1 (sFlt-1) which antagonizes the vasodilator vascular endothelial growth factor (VEGF), and placental growth factor (PlGF). Also, the immune modifier endoglin is a circulating factor in preeclampsia. In the past, placental function tests (e.g. oestrial concentrations), and tests of maternal endothelial function (fibronectin) have been abandoned as unhelpful in diagnosis and unsuitable targets for therapy due to their non-specific nature. These newly recognized circulating factors have specific actions which imply they link endothelial dys-function with placental dysfunction. sFlt-1 links the formation of the placental vasculature and its hypoxia responses to maternal vascular resistance, and endoglin, to the early immunological events of pregnancy.

The pathological phases of pre-eclampsia can be described as pre-clinical and clinical. In the preclinical phase, the aberrant formation or placental invasion of maternal blood vessels occurs. In the clinical phase, the mother responds via endothelial damage with hypertension and proteinuria. The early placental events are immunological and vascular in origin. The result, therefore, is the active inhibition of robust maternal immunity and the invasion of uterine (maternal) spiral

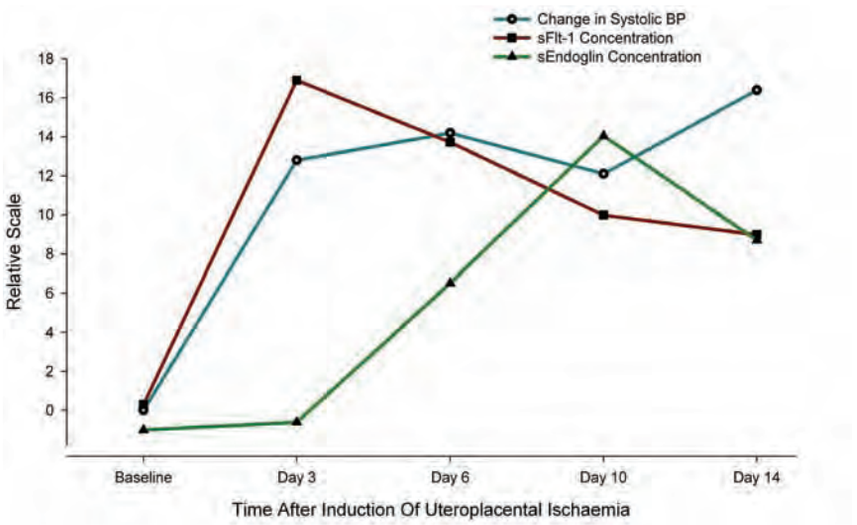

Figure 2. The timing of the rise in sFlt-1 after induced placental ischaemia matches that of the elevation in blood pressure suggesting a causal link. The later rise in serum endoglin represents either a late hypoxic response or activation of the TGB-β1-3 immune axis from an induced inflammatory state.

arteries to form a low pressure high flow system without local autoregulation.

Soluble Flt-1 is the circulating form of the VEGF receptor Flt-1. Binding of VEGF and Flt-1 is responsible for angiogenesis and blood vessel integrity. The central role of sFlt-1 as a mediator of pre-eclampsia is based on infusion studies in pregnant rats (Maynard, 2004). The animals studied subsequently developed renal endothelial lesions and hypertension which were reversible with exogenous VEGF (Li *et al*. 2007). A cause of the elevation in sFlt-1 has been shown by us to be acute placental ischaemia (Fig. 2). This was confirmed recently in rats (Grainger, 2007). Studies of sFlt-1 in banked human serum has shown that elevations occur 3–8 weeks prior to the onset of clinical symptoms (Levine, 2004) suggesting that placental ischaemia later in pregnancy is the probable underlying cause.

Endoglin is the soluble receptor for TGFβ1-3. Receptor activation activates a predominantly immunosuppressive response. In pregnant rat studies, the addition of exogenous soluble endoglin leads to a more generalized endothelial disease than is seen with sFlt-1 alone (Venkatesa, 2006). The cause of any endogenous increase in endoglin is not known, but our data (Fig. 2) would suggest that it is a delayed response to reduced placental blood flow. Studies of human serum suggest that it is elevated up to 3 months prior to the clinical onset of hypertension (Levine, 2006), suggesting either that it is a more subtle and sustained marker of ischaemia much earlier in pregnancy or that the ischaemia is linked to an inflammatory response which builds more slowly. The presence of an early inflammatory aberration being linked with pre-eclampsia is evidenced by many studies of cytokine (Th1/Th2) imbalance and whole animal physiology studies showing that cytokine imbalance in early pregnancy can control maternal blood pressure (Orange, 2005).

It is not known why this immune imbalance occurs in early pregnancy. Whether this is due to innate overactivity of the maternal uterine natural killer cell or other T cells, or whether these cells are overactive as a result of poor immunosuppressor function by the placenta itself is yet to be determined. This immune regulation appears to be linked to the intrinsically low oxygen tension in the uterus. The high incidence of pre-eclampsia in women with intrinsically poor placental blood supply as occurs in chronic hypertension would suggest also that the blood flow is a primary phenomenon. The endothelial dysfunction that results from the up-regulation of molecules such as endoglin and sFlt-1 may be relevant in local uterine artery dysfunction as much as in the profound endothelial disease manifest by such a remarkable and sudden increase in blood pressure.

The incidence of immediate consequences of pre-eclampsia, headache, seizures, renal failure and liver failure are decreasing due to excellent antenatal care, accurate diagnosis and prompt delivery. Support for younger and younger babies by advances in neonatal intensive care have also diminished perinatal loss due to prematurity. The longer consequences to maternal and neonatal cardiovascular health after hypertension in pregnancy are clear to clinicians but as yet not fully understood. However, it is possible that the treatment and timing of delivery and therefore the duration of high blood pressure and endothelial dysfunction, may in and of themselves be contributors to the long term cardiovascular risk via endothelial health.

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Travel grants

As of 31 August 2008, The Society will consider applications for travel grants on a monthly basis. Submission deadlines will fall on the last day of every month (except December). Your application must be received in advance of the deadline that falls at least 1 month before the event for which you seek support.

100 years ago in *J Physiol*

On the relative parts played by nervous and chemical factors in the regulation of respiration. F H Scott (1908). *J Physiol* **37**, 301-326.

Frederick Hughes Scott's paper describes work on anaesthetized rabbits and cats, measuring the effects of the respiratory gases CO_2 and O_2 on respiration and how these effects are altered after cutting the vagus nerves. The paper is an impressive demon-stration of the technical mastery of the *in vivo* experimenters of a century ago. It also offers an insight into the long history of research into respiratory physiology. Experimental physiological investigation of respiration was already at least two and a half centuries old when Scott was carrying out his work, and many of the underlying principles had been worked out by eminent names of the late 19th and early 20th centuries – Haldane, Priestley, Hering, and others – whose work Scott cites in the paper.

Scott's first conclusion would be easily recognizable to anyone who has taught the classic undergraduate physiology lab class with students re-breathing from spirometers or Douglas bags:

'The respiratory mechanism may be stimulated by slight amounts of carbon dioxide or great diminution of oxygen in the inspired air. In animals with vagi intact these lead to an increase of rhythm as well as to an increased depth of respiration.'

And later he summarizes the role of vagal reflexes in respiration:

'Inflation of the lungs, even at the height of dyspnoea, inhibits inspiration and leads to a relaxation of the inspiratory muscles if the vagi be intact. If the vagi be divided, then inflation has no influence on the respiratory movements.'

Scott's paper acknowledges the influence of Professor Ernest Starling, head of the Physiological Laboratory at University College London where the work was done:

'In conclusion I desire to express my thanks to Professor Starling for his advice and for the assistance he has given me with the experiments recorded in this paper.'

This is interesting, since Starling himself never worked on respiration. Indeed, the reason for Scott's studying respiration at all is obscure, since he had no background in respiratory physiology, and published only this single paper on the subject. The paper did, however, earn Scott a DSc degree.

Frederick Hughes Scott (1876–1951) offers an early example of a peripatetic physiology career. Having taken successively his bachelor degree (1897), PhD (1900) and medical degree (1904) in Canada, the country of his birth, Scott travelled to Berlin, one of the key centres of the time for experimental physiology, before working for several years (1906–1908) at UCL. Following these stints as what we would now call a semi-independent postdoctoral research fellow, Scott became a faculty member in yet another country, the USA, at the University of Minnesota in Minneapolis. Here he passed the rest of his scientific career, becoming a full Professor of Physiology in 1918 and retiring in 1944. Scott was in fact the first ever PhD graduate of the University of Toronto, and is commemorated there by an F H Scott lecture, first given in 2000, the centennial of Scott's PhD, by Nobel Laureate David Hubel.

Scott did no further work on respiratory physiology, though he did later publish on the changes in blood pressure evoked by respiratory activity. Much of his later work was on fluid compartments and fluid exchange, a subject into which he might also have been guided by Starling's influence. Scott's most enduring contribution may be two of his earliest papers, from 1905–1906, which contributed to the framing of the concept of neurotransmission. This history, and more about Scott's life, can be found in an interesting article by Hugh Blaschko (Blaschko H (1983). *Notes Records Royal Soc Lond* **37**, 235–247).

Austin Elliott

Fit 4 Life Day

The University of Essex in Colchester, with sponsorship from The Society, hosted a free event, Fit4Life Day during the Easter holidays on 4 April. Many companies, including our journal publisher Wiley-Blackwell, also contributed prizes for a raffle in aid of the British Heart Foundation. Secondary school children, families and individuals of all ages were invited to come along and participate to explore what a healthy lifestyle is, and how it can be achieved. The day was aimed at the over 12s, with the challenges and information sessions linking in with the national science curriculum. Over 250 people attended.

In a series of information sessions running throughout the day, participants found out what happens to the body during exercise, what the Olympics could do for them, how the University is contributing to knowledge about health and exercise, and what a healthy lifestyle is with a myth buster session. They got to question some of the UK's leading health and fitness experts, and met sporting stars, including Paralympians.

Participants tested their fitness levels, and found out how these can be improved, in a variety of physical challenges – ranging from how fast they could run, how high they could jump or how flexible they were. There were also various have-a-go at sports taster sessions, including yoga and climbing. I got nabbed by the Karate teacher for her session (perhaps because I was lurking too close with a camera) and thoroughly enjoyed it. It certainly fixed the cold that I had that day.

The programme on the day was a great success, mainly due to the Herculean efforts of Valerie Gladwell, one of our Council members, and her colleagues in the University of Essex Events Team. Other Society Members also contributed, including Judy Harris(University of Bristol), who ran many of the lab based activities on the day, and Christof Schwiening, another Council member, who brought his family along to participate. The event also attracted the attention of the media with several items in local Essex press (Essex Chronicle, East Anglian Daily Times, and Evening Gazette) as well as mentions on local radio stations (SGR Colchester, Essex FM, BBC Essex, and Dream 100).

A good time was had by all, the point about the relevance of physiological research to sport and health issues was got across to participants, and I now feel very guilty about using the lift in our office building in London. The event certainly got the message across to me, as a commuting mum of a toddler who claims not to have time to join a gym, that relatively small changes in the normal daily routine can make a huge difference to achieved levels of activity.

Liz Bell

The Physiological Society / BPS Joint Medical Training Group

The Society has teamed up with the BPS to look at issues surrounding the effective teaching of physiological and pharmacological principles to medical undergraduates. The Joint Working Group is chaired by Ole Petersen. The first stage of the work will involve developing a core physiology curriculum to complement that already developed by BPS.

Patently absurd?

In the last issue of *Physiology News*, (**71**, 9) Michael Taggart argued that ' commercial potential' is a largely irrelevant and potentially damaging concept when applied to physiological research. As one who was actively engaged in physiological research in both an academic context (at the universities of Leeds, Yale, Montréal and Manchester) and in an industrial context (at Unilever's R&D facility) I beg to differ. If asked what the point of their research is I suspect (based on experience) that a significant proportion of physiologists would answer that it is either 'interesting', or part of a career progression.

Funding for scientific research is a scarce resource and should be viewed as an investment. As with all investments, choices have to be made. The question that is on the lips of those who have funds to provide is 'What will the return on my investment be?' (possibly worded as 'What is the significance of the research for prosperity and quality of life?' in the BBSRC grant proposal cited by Mike Taggart). The idea that a reviewer can answer with ' How can one possibly tell? I decline the offer to indulge in the usual bullshitting' smacks of the most appalling arrogance. Faced with this attitude, will it be surprising if taxpayers ask: 'Why should my taxes be spent on research for which there is barely an assumption that any benefit will ensue?' Indeed, if the scientific foundations of much of modern medicine can be traced back to a gentleman's dining club founded in 1876, perhaps physiological research doesn't need public funding at all for us to reap its benefits! A contrasting view is that publicly funded physiological research can and does have an impact on prosperity and quality of life. To gain public (and financial) support the challenge for physiologists is to clearly articulate this impact. My view is that the physiologist who is unable to lucidly explain the anticipated or hoped-for tangible benefits of their research (either in economic or quality of life terms) suffers from either an excess of self-indulgence or intellectual laziness.

Jon Beck
Anthemis Consulting Ltd,
Macclesfield, UK

Michael Taggart responds:
Jon Beck makes many decent points. As someone who reviews and writes innumerable grants, is a member of the British Association for the Advancement of Science and who has recently spoken to MPs at the House of Commons about funding for scientific and medical research, I think I have a fair idea of our obligation to engage with the public on matters of research justification. Perhaps our different interpretations of the anonymous reviewer's comment that I quoted in my article, and which irked Jon Beck so, relates to expectation.

I wholeheartedly agree that, as Jon Beck mentions, '*publicly funded physiological research can and does have an impact on prosperity and quality of life*', but would venture that anyone engaged in such activity knows full well that the benefit is often accrued over several years, and numerous rounds of grant funding, and arises from the efforts of many. I therefore interpreted the reviewer's comments not as though they '*smacked of the most appalling arrogance*', but rather the opposite – that they reflected an honest appreciation of the more modest outputs accomplishable by scientific endeavour, coloured by a frustration that a government-backed Research Council sought justification for research in such simplistic terms – this last being something that serves, as anyone who often reviews grants will recognise, to encourage short-termism and inflated claims of importance. Perhaps when the red mist clears Jon Beck will consider that '*good work that leads to better physiological knowledge ... that is the basis of good medicine*' is a concise, lucid and accurate description of much scientific research that makes a beneficial contribution to society.

I am writing to let you know how much Michael Taggart's article echoes the views of many scientists. Perhaps this discussion about 'intellectual property in science' deserves to become an issue for a national (and even international) debate.

Taggart argues that the current obsessive trend for commercialisation of our research, and for patenting of whatever we may discover, is counterproductive and in some ways goes against the ethos of scientific investigation. I agree totally.

There are a couple of extra points which could be added to the argument. One is that, even if a scientist becomes the owner of a 'good' patent which eventually gets commercialized, the share of the wealth which the 'inventor' gets is typically miserable. Most of the wealth goes to those who lent the money, as you can hear from anyone who has gone this route. Are we then forced to give the lenders (who are not poor) yet another chance to get rich? Or should we stick to producing knowledge, which is actually our ultimate goal?

Another point is that no-one has come up with a convincing financial justification for the recent explosion of business development / technology transfer / patent offices in UK universities. In my own university we now have over 50 permanent employees in this area, where once there were a handful. Another example: if one takes one of the universities that actually make clear how many people are employed in 'research business development' – and many do not – the contact directory for the relevant department at the University of Bristol has almost 60 names[1].

Presumably the justification for this uncontrolled expansion is the possibility of financial benefit. But are these offices actually generating

[1] http://www.bristol.ac.uk/research/contact

more money than they cost? I simply cannot believe it.

Instead, the financial burden of this sort of set-up will have a detrimental impact on science. This is because Enterprise Development offices 'eat' money which otherwise could have been used to pay and support researchers. Much of this money presumably comes to universities in the first place in the shape of overheads on research grants.

It is great that Michael Taggart and *Physiology News* have started this discussion. I hope there will be a way to take it forward and bring it to the attention of the decision makers.

Name and affiliation supplied

Journal Club

The Journal of Physiology has recently introduced a Journal Club feature. Articles will be short reviews by graduate students, post-doctoral fellows and other training level scientists of papers from recent issues of *The Journal of Physiology* (http://jp.physoc.org) or our publish-ahead-of-print Physiology in Press (http://jp.physoc.org/physinpress.shtml). These reviews can be the result of formal laboratory journal club discussions or informal discussions among interested parties. Multiple authorship is encouraged. The articles should consist of a brief background, a brief presentation of the data of interest and a very brief discussion of the significance or a specific aspect of the paper. See *The Journal of Physiology*'s Instructions to Authors for full details (http://jp.physoc.org/misc/ita.shtml).

Science in the media – not all as it seems ...

Natasha Hausman reports on a new series of workshops organised by *Sense about Science* to highlight how other young scientists can get involved in promoting good science

Science in today's society is regularly under the media spotlight. We hear reports ranging from the development of hybrid embryos to new-found miracle cures for cellulite. Yet with the increasing popularity of science have come more dubious, pseudo-scientific claims. So who, or what are the public to believe?

The *Voice of Young Science* (VoYS) network was set up as part of *Sense About Science*, a registered charity committed to promoting good science and evidence for the public. The VoYS network is running a series of workshops to help early career scientists become aware of the media spotlight on research, as well as help them to deal with the media should the need arise. On 6 June, I attended one of these workshops where 35 PhD students and post-docs gathered at the Institute of Biology for a *Standing up for science* workshop.

The first session of the day involved three scientists describing how they had made a positive impact in their field through positive communication with the media. This was followed by an open and informal discussion with the audience.

Stephen Keevil (Consultant Physicist, Guys and St Thomas's Hospitals) explained how his and others' communications to the media about the values of magnetic resonance imaging (MRI), a powerful diagnostic tool, allowed a critical debate on its use to be re-opened. MRI was about to have its use limited under the Physical Agents (EMF) Directive, and this positive communication via the media had a great impact on what could have been a closed case.

Azra Ghani (Reader in Infectious Disease Modelling, Imperial College) discussed her considerable experience with the media as part of her work on BSE/vCJD. As we are all aware, BSE/vCJD has, in recent years, been a subject of public panic as a result of negative media coverage. Ghani talked about how correct communication with the media can turn a negative story into a sound, scientific story. The media need headlines to sell papers and the way in which information Is delivered to them can be critical to the way the story is told.

Robin Lovell-Badge (Head of the Division of Developmental Genetics, MRC National Institute for Medical Research) regularly comes into contact with the media. His research areas include early embryonic development and the use of stem cells, often deemed controversial issues by the media and the public. He encouraged the audience to talk about their work, to explain and justify why scientists use particular techniques and perform certain experiments so that the media and public can develop an informed viewpoint. An area of concern for many young researchers is whether they should openly discuss the use of animals in research. The overall consensus was that if scientists talk about the use of animals, and can highlight both the important scientific outcomes the work will bring and the tight regulations and procedures involved, then perhaps this important area of science can become more widely accepted.

A panel of three journalists led the second session of the day. Members of the audience could all think of examples of badly reported science and were eager to voice their opinions on the matter. Lewis Smith (Environment and Science reporter, *The Times*) went on to explain that his job is to report science in a way the public will find interesting and entertaining, as even the best scientific articles do not make for family-friendly reading.

It was suggested that scientists are actually in a better situation (in terms of media science reporting) than in years gone by. Mike Swain (Science and Environment Editor, *Daily Mirror*) described how just over 2 years ago his newspaper did not have a science reporter. Tom Fielden (Science and Environment Correspondent, *Radio 4*) reiterated this, explaining that news and radio have not always employed science correspondents, yet now there is this greater outlet for research to be brought into the public domain. Hearing from the journalists put their role into a new perspective, and highlighted the positive influences the media can have in reporting science. Scientists will have to learn to 'trust' the media, but obviously that means telling them the story in a way they can sell it in a positive way - stories need to make headlines and, if you can't make the story have a positive impact, beware!

In the last session of the day we heard from the people directly involved with *Sense about Science* and VoYS. Considerable work has been done by VoYS on challenging the more dubious scientific claims used to sell products from detox patches to pendants that protect from the effects of electromagnetic radiation. Most offending companies simply do not expect to be challenged about such claims, but else how are young scientists to stand up for science? Simon Levey (Science Media Centre) discussed the possibilities of media training for researchers. With good preparation and a thorough understanding of the key messages to put forward, early career researchers can stand up to be heard. PhD students and post-docs are specialists in their fields of research, making them more

qualified than most to comment when called upon.
The close of the workshop was followed by a trip to the local pub, with both participants and panellists continuing discussions from the day. It was an excellent opportunity to meet the other researchers properly, to find out about their own work and experiences. VoYS are flying the flag for good science for the public, and young career researchers can help ensure that the public view-point on science is an informed view-point. I would thoroughly recommend you try and get yourselves a place on one of these workshops as they really do give you the confidence to believe in your work and stand up for what you do.

Natasha Hausman
2nd Year PhD student, University of Manchester, UK

The next *Standing up for science* workshop will be held in Edinburgh on 21 November. VoYS are currently working on the following projects:

- *Standing up for science II – the nuts and bolts*. Many early career researchers are enthusiastic and want to get involved in raising the standard of evidence in public debate, but some of them are not in a position to communicate their research to the media or are unaware of what other activities they can do. VoYS are putting together a booklet to inspire others to stand up for science by giving them examples of their own experiences and advice on how to do it, and are looking for help with writing and reviewing the booklet.
- *Inspire your peers* pack. This initiative was developd to help VoYS spread the word about how to stand up for science and evidence in public. If you would like a copy of the pack, or would like to sign up for a demo talk please contact Alice.
- *There goes the science bit.* VoYS are currently looking into the evidence behind other products.

If you are interested in being involved in any of these projects, or for further information on the workshops, contact:
voys@senseaboutscience.org
or visit
www.senseaboutscience.org/VoYS

Where next?

The difficult career options at the end of a PhD

Coming to the end of my PhD, I'm starting to sympathise with the Alzheimer's model mice in the Morris water maze, searching for a platform that must be there but with no idea how to locate it. I can't keep changing direction forever so this is really the biggest decision I've ever made, affecting my entire future career. I have an undergraduate degree in molecular biology, with a year in industry, followed by a PhD project in neuroscience (which I am in the late stages of writing up). But what comes next? I love both research and science, enjoy communicating my work to both scientists and non-scientists and love the buzz when experiments work and results are good. But I also love working in a fast paced and changing environment, being in direct competition and meeting deadlines. I need to find a job that encompasses all these things and I am starting to panic about my future.

To try and get things into perspective I attended a *Professional development day for early career scientists* organised by the Newcastle University Careers Service. I hoped to turn up and find a career ideally suitable for me, but I came away more than a little confused, mainly because there seem to be no straightforward career options. The day was divided into personal insights from people with varied careers within academia and careers outside academia.

The academic perspectives came from a young lecturer who told of her three postdoctoral positions followed by a lectureship. She had to wait for someone to leave before she could get a lectureship and the postdoctoral positions had been lucrative in terms of publications but detrimental to her personal life, as she had to live for 5 years at the opposite end of the country to her partner. Another postdoctoral researcher also said that it was critical to be flexible about location. Both highlighted the stress of grant renewals every 2–3 years and the uncertainty of any definite future in one position. A more senior researcher told of his successful commercialisation of his research and development of a company. He had struck gold because of it but how many people can be that lucky? Even he mentioned the stress of grant renewals because of the responsibility for his group who are paid by the grants. So, possible career number one: academia, with upheavals and financial stress every 2–3 years.

From outside academia, industrial researchers talked of their experiences within a company. It was very positive, with a multidisciplinary team environment and the aim to develop new drugs. All well and good but we all hear the rumblings of empty pipelines, ending patents and imminent redundancies that accompany them regularly. So, career option number two: industry, with little more security than academia.

Outside research, a medical writer, a patent attorney and a scientific recruiter described their jobs. All sounded interesting and fast moving but I'm not sure I want to leave my science behind. Career option number three: leave science completely.

I hate to be negative but, in doing a PhD, we all think/hope we are training to be highly competent and specialist in our areas of research. Granted it will be years until we can expect to be leaders in the field, but we are highly skilled individuals who work in critical areas of medical research. Is it too much to ask that we have job security to match our skills levels? I don't know any other area of work with qualified people involved but such a low level of security. Something fundamental seems to be missing in the system. Surely the most beneficial part of training people to PhD level, and investing so much money in it, is to keep them in research. Is it any wonder that so many leave research when the career options and job security, never mind the pay packets, are so much more fruitful away from it?

For the moment, I am still swimming in the options - I only wish that the careers paths available had less negative sides to them.

Fiona Randall

Education activity at The Society

The Physiological Society has an active education department, which aims to promote physiology, and facilitate teaching and learning within the discipline.

The table opposite provides a summary of The Society's education-related activities and resources, all of which are free, and reports of activities regularly feature in this magazine. The table also indicates the many collaborative efforts with other learned societies and organisations. These combined efforts are particularly apparent when considering the resources and activities available for school students and teachers. For these groups, we focus more on engaging students in science and motivating them to study at a higher level. By combining our resources with other societies, we hope that we can have a greater impact on a larger audience than we could target alone.

The Society is continually researching new ideas, funding new projects and developing new resources in order to strengthen our education portfolio and make physiology accessible to a wider audience. The new Practical Biology website, which is being developed by the Biosciences Federation in collaboration with Nuffield Curriculum Council, is an example of a new project we are supporting and has been highlighted in the article on p. 42.

If you have any questions about any of the resources or activities please contact education@physoc.org.

Audience	Activity	Meeting	Resource
School students	Sixth form workshops	[1]BA Festival of Science	[1*]Future Morph
		[1]National Science and Education Week	[1]Biology – a subject for life
		[1]UCAS conventions	[*]Careers leaflet for Key Stage 3 and 4
			Understanding Life
School teachers		[1]Annual meeting of the Association for Science Education (ASE)	[1*]Practical biology website
			[1]Animals in research: make up your own mind
Undergraduates	Funding for undergraduate seminars (part of Departmental Seminar Scheme)	[1]Life Science Careers Conferences	Where next careers advice
		Young Physiologists' Symposia	[1]Animals in research: make up your own mind
	Undergraduate Prize for Physiology		[*]Undergraduate members' handbook
	Astra Zeneca Prize for Undergraduates		
	[2]Short-course workshops		
	Vacation Studentships		
	[*]Grants available for meeting attendance		
Undergraduate physiology teachers	[*]Teaching Prize	Teaching symposium at main meeting	[*]Philter
Early-stage physiologists	[2]Short-course workshops	[1]Life Science Careers Conference	[1]Animals in research: make up your own mind
	Funding to organise Young Physiologists' Symposia	Young Physiologists' Symposia	
	Grants available for meeting attendance		

[*]Coming soon
[1] In collaboration with other societies/organisations.
[2]The Society runs short courses in *in vivo* techniques, RT-PCR and microelectrode techniques.

Physiology on the move!

In 2007 the University of Bristol acquired a purpose-built HGV-sized Mobile Teaching Unit (MTU), which was funded by the Applied and Integrated Medical Sciences Centre for Excellence in Teaching and Learning (AIMS CETL). The MTU is being used very successfully to take physiology out to schools and into the community. It expands when stationary to create a self-contained teaching venue, complete with high-quality audio-visual facilities, which can accommodate up to 20 participants. It also functions as a stand-alone laboratory in which a generator supplies power, heating and running water, enabling us to bring biomedical science literally into the field!

Interactive teaching sessions for students aged 5 to 18 are run by members of the Departments of Physiology and Pharmacology and Anatomy at Bristol University, led by Lauren Hughes. The sessions give students hands-on experience of human physiology as the MTU contains all the equipment required

Come and join us at the BA Festival of Science

Following the success of last year's cystic fibrosis event at the Royal Society, we are holding it again at the BA Festival of Science in partnership with the BSF, EuroCareCF and the Society for General Microbiology.

For more information on this and other events being organised by the BSF at the Festival as part of the Biology Road Show, see the advertisement on p. 49. Book online at www.the-ba.net/festivalofscience or phone 020 7019 4947.

External view of the MTU (above) and a session on the heart for years 5 and 6 (below).

to carry out lung function tests, to record physiological parameters such as ECG and blood pressure, and to study the effects of electrical stimulation of nerves and muscles. The MTU is proving very popular with schoolchildren and their teachers as it provides a novel learning environment, delivered to the school doorstep, which gives students access to equipment that is rarely available in the classroom.

Since its launch, the MTU has visited over 30 schools, mainly in Bristol and the surrounding area, but it has also travelled farther afield to London and, in March 2008, it visited Jersey as part of the island's first ever Science Week. So far this year, the miles clocked up by the MTU have allowed over 1700 students to experience 'mobile', hands-on physiology and several schools have already booked return visits. The MTU is also a regular visitor at local science festivals offering members of the public a unique opportunity to explore how their body functions. For more information visit http://www.bris.ac.uk/cetl/aims.

Lauren Hughes
Judy Harris
Department of Physiology and Pharmacology, University of Bristol, UK

Practicals in schools

Why do we need them and what are we doing to support them?

The British Pharmacological Society (BPS) and The Physiological Society acknowledge the importance of practical biology teaching at all key stages in motivating and inspiring the next generation of scientists. In recognition of this, the two societies are working together in a joint venture to support the Biosciences Federation (BSF) and the Nuffield Curriculum Centre (NCC) in the development of a web-based resource of practicals for schools. The societies are jointly represented on the Steering Committee by Judith Hall (Education and Training Manager, BPS).

Why we need to get involved

Concerns over the amount and quality of practical skills taught in schools and sixth form colleges, particularly core laboratory skills, have been raised by employers, school inspectors and colleges of higher education[1]; this is despite practicals being cited by students as one of the most enjoyable elements of studying science and the reason they choose to pursue a career in science. Some of the reasons suggested for the decline in practicals taught in schools include: health and safety concerns of teachers; cost; time restraints; a lack of technical support; league tables and teacher confidence.

To address some of the shortfalls in practical biology teaching, the BSF/NCC is establishing a website[2] to help teachers in schools and colleges to deliver affordable and reliable practicals to pupils from key stage 3 to A level. The biology website follows the launch of similar websites already up and running for chemistry[3] and physics[4]. Advice on content and contributions, including ideas for practicals for the site, are being sought from a wide range of stakeholders including: teachers; learned societies, medical charities and funding bodies; employers; authors; examiners; university and industrial scientists and lecturers.

The benefit of teaching a consistent quality and appropriate range of practicals in schools is clear. Practicals:

- are core to teaching science; biology is an experimental subject;
- aid development of problem solving and analytical skills;
- stimulate original thought and creativity;
- promote collaboration and discussion within and between peer groups;
- foster a life-long interest in biology;
- encourage a career pathway in science.

The future

BPS and The Physiological Society hope this project will achieve the same level of success as the practical chemistry and physics sites. The physics site, launched in January 2004, has a bank of around 650 practicals and receives in excess of 30 000 unique visitors per month, typically viewing a total of 250 000 webpages – testament to the need for such a resource.

The practical biology website will be launched on 22 September 2008. BPS and The Physiological Society are keen to ensure that all biomedical disciplines are adequately represented on the site. If you have any recommendations for practicals for inclusion or any other suggestions please e-mail Jude Hall (jmh@bps.ac.uk) who can forward ideas to the Steering Group.

Jude Hall
Education and Training Manager, BPS
Chrissy Stokes
Head of Education and Membership, The Physiological Society

[1]http://www.bsf.ac.uk/responses/Enthusing.pdf
[2]registered domain: www.practicalbiology.org
[3]www.practicalchemistry.org
[4]www.practicalphysics.org

Practicals in schools – a teacher's view

As a biology teacher I find that a number of students who take biology at A-level do so because they believe it is an 'easy'

option. However, A-level biology is not easy and students find the new vocabulary and practical classes challenging.

At GCSE, practical classes are limited by time, cost and resources and so teachers become constrained to teaching facts and figures, which the student can regurgitate without the need to understand the underlying concept. As a result, students arrive in their A-level biology class with many misconceptions and it takes time to retrain them to think like a scientist.

Some misconceptions have developed through the repetition of experiments at Key Stages 2, 3, and 4. Each time a student is presented with the same experiment, they realise they have seen it before and rather than develop their understanding they recall the results and regurgitate the facts – this doesn't help with the independent thinking that we need to develop in our A-level science students.

As a former scientist, working in academia and in industry, I am only too aware of what these students are missing out on in terms of practical classes. After all, it is the practical classes that will keep students motivated and wanting to carry on until university. Not only that, but it is new and exciting practical classes and concepts that will enable students to develop an inquisitive, scientific mind.

Providing practical equipment for the whole class to undertake an experiment is expensive and, with prescribed practicals for the new type of coursework, it is even more difficult to justify spending money on consumables that can be used only once and will not contribute to coursework.

With improving IT and internet resources, it has become possible to show students videos of other scientists carrying out practicals; though this type of learning has its place, it should never be a substitute for hands on experience. Students like science because it is a practical subject, and reducing practical work by allowing students to sit and watch videos is not a satisfactory solution. Interactive computerised virtual labs are a start but, to keep students motivated and interested, we need opportunities and ideas for cheap, easy and effective experiments that can be done at school.

Catherine Bleasdale
Biology teacher

Practicals in schools – a student's view

As an A level student who has just finished studying biology at a 6th form college, I have always enjoyed the hands-on element of learning. Over the two years at college, I took part in a number of different practicals, which varied from simple experiments, like finding out what blood group I was, to more complex procedures, like studying the effects of different light wavelengths on the rate of photosynthesis.

In biology, I would say I took part in a practical once every 2 weeks, maybe even less than that. Being someone who learns better visually, I felt this was not enough and would have liked to have seen more practicals in biology.

I completed practicals in a number of different group sizes and also worked on my own for some practicals. From my experience I found group work more stimulating, as the experiments were normally more complex, and allowed ideas to be bounced off each other.

Personally, I felt experiments where I knew the outcome were not as enjoyable; as I already knew the answer, I had nothing to achieve or learn by doing the experiment. I found it far more exciting to discover answers myself or as part of a group.

The majority of practicals I completed when studying A level biology were based on plants, which can become tedious after a while and I would have liked to have studied more animal based practicals.

For the coursework element of A level biology, we had to complete an assessed experiment. One of my assessed experiments looked at the rate of reaction of two different sources of amylase on the hydrolysis of starch. I enjoyed the aspect of planning the experiment and then concluding and evaluating the results, but did not enjoy being assessed under practical conditions. I felt it put pressure on the procedure of the experiment and I also felt rushed to complete the experiment. More experiments where the student is allowed to plan their experiment would help students to understand and remember the topic more clearly.

Overall, when I completed a practical on a certain area of biology, I understood and remembered the topic much better. Practicals helped me to create a picture of the processes happening in biology and helped me revise during the exam period. I certainly enjoyed the practical side of the biology course the most and would have liked to take part in more practicals in biology. The practical side of biology definitely motivated me to continue studying science and go to university. I am hoping to study sports and exercise at the University of the Bath, with the view of going into research for human physiology.

Tom Carrington Smith
A-level student

A version of this article will also feature in Volume 1, Issue 2 of the British Pharmacological Society Members' Newsletter, *Pharmacology Matters*.

Undergraduates

Write an article and win £500!

AstraZeneca is generously supporting the career development of undergraduates studying physiology as part of their degree with two annual prizes for the best physiology-related articles written by undergraduates and published in *Physiology News*.

Undergraduate students are invited to write articles, suitable for publication in *Physiology News*, on topics which might include (but are not limited to):

- summer/final year degree projects;
- experience of attending a workshop or conference;
- what turned you on to physiology;
- topical/current physiology-related news items;
- outreach activities (e.g. school visits, science festivals);
- research groups/activities within the department;
- review of a paper that encouraged an interest in physiology.

Articles (up to 1000 words with an optional illustration) should be submitted by 1 September or 1 March.

Submissions should be sent to education@physoc.org and will be judged on appropriateness of topic and writing style by The Physiological Society's Chief Executive Officer, the Education and Membership Manager and a member of *Physiology News* Editorial Board, with agreement from AstraZeneca on the winning article.

Each prize will be £500 and a day visit to AstraZeneca's HQ in Alderley Park, Cheshire (to include UK travel, dinner and overnight accommodation). Full details are available from Mike Collis at mcollis@physoc.org.

The Journal of Physiology

New Editors

The Journal of Physiology recently welcomed new Editors Glenn Toney and James Duffin to the Editorial Board. Glenn (right) received his BS from Weber State University (Ogden, Utah), and his PhD from the University of Louisville (Kentucky). In his doctoral work he studied hypothalamic actions of the peptide neurotransmitter/hormone angiotensin II to increase arterial pressure through recruitment of neuroendocrine and sympathetic neurons. That work helped to delineate the relative contributions of AT1 and AT2 receptors, which had only recently been discovered. During his postdoctoral fellowship with Steven Mifflin, he investigated somato-visceral integration by neurons in the nucleus tractus solitarius (NTS) and identified sensory modalities conveyed to the NTS by hindlimb skeletal muscle afferent inputs. Glenn joined the Department of Physiology at the University of Texas Health Science Center at San Antonio in 1998, where he is currently an Associate Professor. His research focus is on feed-forward and adaptive responses (plasticity) of hypothalamic and brainstem sympathetic control circuits in cardiovascular disease.

Symposia

The next *Journal of Physiology* symposium, *Chloride channels: insight into function from human disease*, takes place on Saturday 18 October 2008 at the Joint Meeting of The Physiological Society and the Chinese, Canadian, Australian and American Physiological Societies in Bejing, China. To register please visit http://www.surveymonkey.com ...

Other forthcoming symposia

Friday 14 November (13:00–18:00)
Mechanisms of neocortical development
At the Society for Neuroscience, Washington, DC, USA.

Impact factors

The 2007 impact factors (IF) were released in June and have risen again for both Society journals. There is considerable divergence of opinion about the significance of this measure of journal quality, but author surveys continue to confirm that a journal's IF is among the most important considerations in choosing where to publish, and the Editorial Boards of both journals are conscious of the need to maintain a competitive IF in order to attract good papers.

The Journal of Physiology's IF rose from 4.04 to 4.58. Other metrics published along with the IF confirm *The Journal*'s improving status; its ranking in the ISI Physiology list has risen from 9th out of 76 journals to 6th out of 78, and the half-life of *Journal* articles remains high at 9.2 years (9.1 years in 2006). *The Journal* published around 1000 original research papers and 100 commissioned review articles during the 2 year period recorded for the impact factor, so changing the impact factor substantially is a long-term exercise. The Editorial Board remain committed to publishing only the highest quality research in physiology and hope to see this reflected in a continuing rise in the impact factor over the next few years. For details of *Experimental Physiology*'s impact factor see p. 45.

18–21 March 2009
Altered placental functions as a cause of altered fetal growth
At Society for Gynaecological Investigation, Glasgow, UK.

18–22 April 2009
The world within – impact of the intestinal microbiota on whole body physiology and pathophysiology
At Experimental Biology 2009, New Orleans, LA, USA.

6–10 July 2009
Novel insights into oestrogen actions
At The Physiological Society Annual Meeting, Dublin, Republic of Ireland.

31 July 2009 (10:00-12:30)
Dynamic aspects of functioning membrane proteins
31 July 2009 (10:00–16:30)
Physiological regulation linked with physical activity and health
At IUPS, Kyoto, Japan

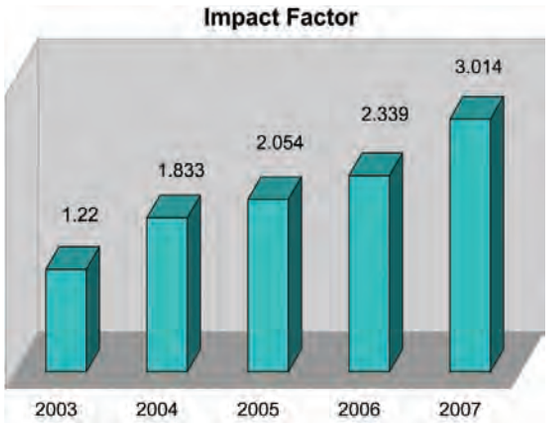
Experimental Physiology

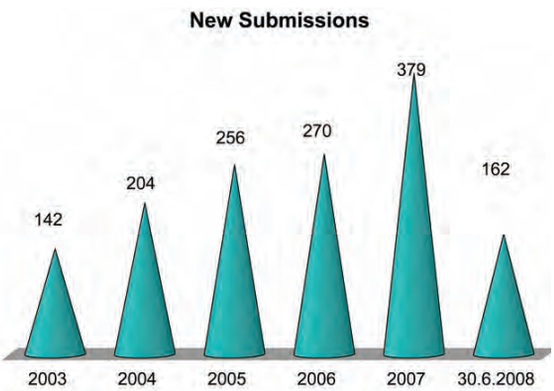
100 Years 1908-2008

To celebrate the journal's centenary David Paterson (centre) hosted a dinner at Peterhouse, Cambridge for previous Chairmen and others who have been involved with the journal (*from left to right*): Julian Paton, Cecil Kidd, Peter Mott, Emma Ward, Ann Silver, Carol Huxley, Ole Petersen, John Coote, Ian McGrath and Michael Spyer.

100 years of *Experimental Physiology* Chairmen. *Top row* (*from left*): Founding Editor EA Sharpey-Schafer (1908–1934), I de Burgh Daly (1935–1948). *Second row*: JH Gaddum (1949–1950), D Whitteridge (1951–1968). *Third row*: RB Fisher (1969–1972), WE Watson (1973–1980). *Fourth row*: CR House (1981–1986), C Kidd (1987–1994). *Fifth row*: JI Gillespie (1995–2000), JH Coote (2001–2006). *Above*: Current Chair DJ Paterson.

A full report on the state of *Experimental Physiology* in it's centenary year is available in the January issue[1]. The Editorial Board are pleased to be able to update the Impact Factor chart to include 2007 (right) and show another rise, taking it over 3 for the first time. The increase in submissions continues (right).





Experimental Physiology was pleased to sponsor three symposia from The Physiological Society Meeting in Cambridge in July:

Cotransmission in the autonomic nervous system
Chris Johnson & Anja Teschemacher

Endothelial aging: molecular mechanisms and functional significance
Margaret D Brown & Richard CM Siow

Mouse models for human epithelial disease: novel insights and new horizons
Peying Fong, Paul Sharp & Mike Gray

Reports from these Symposia and the lectures listed (right) will be published in *Experimental Physiology*.


QUARTERLY JOURNAL OF EXPERIMENTAL PHYSIOLOGY

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Apologies to David Eisner who took the photo of David Paterson promoting *Experimental Physiology* in New Zealand and was not credited (*Physiology News* **71**, 53).

[1]http://ep.physoc.org/cgi/content/full/93/1/1

Joan Mott Prize Lecture
Hormones as epigenetic signals in developmental programming
Abigail L Fowden
(University of Cambridge, UK)

Sharpey-Schafer Prize Lecture
Gas channels
Walter F Boron
(Case Western Reserve University, USA)

Paton Lecture
To breathe or not to breathe? That is the question
K Michael Spyer
(University College London, UK)

The Society website – to launch and beyond

In the spring issue of *Physiology News* (**70**, 12) I highlighted the planning and development phase of the new Society website. I am pleased to announce we have now launched the site, which is proving very successful with our members, Society staff, fellow societies, and the public in general. After an extensive period of final testing and fine tuning, the website went live during March 2008, with all Society Members being emailed their login credentials and invited to explore the new site.

Since this initial launch we have been monitoring visitor movements over the site. Here is a summary of visitor statistics since the March site launch:

Traffic summary

- Number of distinct visits 11 036
- Average minutes per visit 5.5
- Average page views per visit 25
- Number of files downloaded 3886
- 4725 distinct web pages have been viewed a total of 283 114 times

...and here is some statistical information recorded during a typical week in May 2008:

Top five sections

- Homepage
- Scientific Meetings
- Membership
- Member area
- Journals

Geographical visitor origins

- North America 45%
- Europe 39%
- Asia 12%
- Oceania 3%
- South America 0.3%
- Africa 0.7%

Top 10 referral sites

- www.google.com
- www.google.co.uk
- www.ithaca.edu
- www.physiology2008.org
- http://en.wikipedia.org
- www.munax.com
- www.blackwellpublishing.com
- www.sportsci.org
- http://search.yahoo.com
- www.bubl.ac.uk

We have also seen a very positive uptake in the use of our online membership application and renewal

Liam McKay.

features since the launch:

- New membership applications 80
- % of all new applications 95%
- Online membership renewals 200
- % of membership renewals 100%
- Grant applications 75
- % of grant applications 95%

These figures are very encouraging and show that the ease of online processing is proving a popular option for our Members.

From an office staff perspective, the website has made significant improvements in the administration of membership applications, renewals, and grant applications. We have seen a significant reduction in the amount of administration time taken to complete these tasks, whilst greatly increasing both the accuracy of our data and the turnaround time of applications.

This month we opened online registration for our Oxford meeting and hope to experience a similar level of success – early signs are encouraging.

Another measure of the website's success has been the level of interest expressed by other societies. Since the site launch I have met with a number of scientific and non-scientific societies interested in pursuing a similar website project. Aside from being very flattering for The Society, this will really aid us in building inter-society relationships and could prove a useful pool of shared knowledge and experience in the future.

No project of this scale would be complete without some minor problems. We found that our Forums (online discussion boards) in the Members' area haven't been used. We had hoped that these boards would be a useful area for our Members to discuss a variety of topics in an open, yet secure, online environment. Perhaps nobody wants to be the first poster! I would like to encourage our Members to visit our forums and create new discussions or contribute towards existing ones. However, the Member and Committee directories are proving to be a very popular resource for communicating with fellow Members.

We have been very pleased with the launch and ongoing use of The Society website. It is very encouraging to see so many visitors utilising so many aspects of the site.

Future plans

As well as the continued development of content, we have a number of future enhancements planned:

- Renewals – automatic membership renewals reminders and subscription lapsing;
- News enhancements – enhancing the display and delivery of news (including an eNewsletter for Members and RSS feeds);
- Mailing lists – subscription to a variety of mailing lists through the MySite area;
- Sage / database integration – allowing us complete integration of our membership database with our accounting software.

I would like to encourage all our Members to visit the site to obtain the latest Society news and information, to contribute to the online forums, and to update their online member profile.

I would also like to hear your feedback on the site. Please email your comments or suggestions to lmckay@physoc.org

Liam McKay
IT & Communications Manager

Annual General Meeting

The Society's AGM was held during Physiology 2008 in Cambridge. The AGM was well attended by Members and there were some interesting questions from them. The meeting was chaired adeptly by Bill Harris, head of the host department.

Two formal resolutions proposed and supported by Council were passed with clear majorities. One was to reduce the time an individual had to be a Member before they can nominate a new Member. Additionally, nominations for membership will now be reviewed and approved in the office and only referred to the Executive Committee in questionable cases. Some concerns were raised about the lack of membership involvement in the process and the potential for an increased risk of infiltration of The Society. However, it was pointed out that there are experienced Members of The Society in the office and, as no Members present could think of additional ways to ensure security over and above those already in place, the resolution was passed.

The other resolution concerned scientific meetings: the removal of the need to introduce non-Members, the introduction of registration fees for Members and confirming that the quality of abstracts was the responsibility of the author and not The Society. (Submitted abstracts are accepted, rejected or accepted as title only in the situation where the science appeared solid but the English poor. The only reason that abstracts will be returned to authors for correction will be to clarify ethical issues). This resolution was passed by the meeting, after some discussion and clarification that registration fees would not apply to Affiliates or student members of a host department, providing that these individuals registered for the meeting by the early bird deadline. A generous proposal from a retired Member that this group should not be exempted from paying registration fees was politely rejected.

As well as approving (or not) resolutions made by Council, the AGM is an opportunity for Members to propose matters for discussion. What is put in the AGM agenda for discussion is the prerogative of Council as there clearly needs to be a process to weed out motions that are not appropriate, factually incorrect, or in the extreme, potentially libellous. Allowing Members to put forward matters for discussion is seen as good practice, but there are some other important caveats to this process. A Members' proposition cannot be treated as a resolution (and any vote on it be binding on The Society) unless 5% of the membership have supported the proposal at the time of submission. This is a common sense rule (and company law) to prevent the undermining of Council who are, of course, the elected representatives of the membership. Without such a rule, a few individuals could push

Council 2008–2009

The Society's Council now consists of 19 Trustees and two Affiliate representatives:

Clive H Orchard* (University of Bristol) – President
K Michael Spyer* (University College London) – Deputy President
J Graham McGeown* (Queens University Belfast) – Treasurer
Prem Kumar* (University of Birmingham) – Meetings Secretary
Louise Robson* (University of Sheffield) – Chair, Education Committee
Jeremy PT Ward* (King's College London) – Chair, External Relations Policy Committee
Jonathan F Ashmore (University College London)
John W Hanrahan (McGill University, Montreal)
Christof J Schwiening (University of Cambridge)
David Sugden (King's College London)
Alexei V Tepikin (University of Liverpool)
Teresa Tiffert (University of Cambridge)
Valerie F Gladwell (University of Essex)
David JA Wyllie (University of Edinburgh)
Godfrey L Smith (University of Glasgow)
John Winpenny (University of East Anglia)
John C (Ian) McGrath (University of Glasgow) – Chair, Publications Committee
Patricia de Winter (University College London)
Susan Jones (University of Cambridge)

Affiliate representatives
Patrick Howorth (University of Bristol)
Jane Cleal (University of Southampton)

* Trustees marked with an asterisk are also members of the Executive Committee.

Contact details for Council members and further information about all The Society's committees can be found in the Member area of our website.

binding resolutions through against the wishes of the governing body and the majority of the membership.

A number of matters raised by Members were discussed. Abstract reviewing came up again with a motion from a Council member, Christof Schwiening, that gave four options, ranging from going back to the old days of voting to having no review process at all. There followed a lively debate and a small majority of those at the meeting were in favour of retaining the current system of review by SIG conveners, but allowing them to correspond with the authors of abstracts to help them to improve the quality. If implemented, this will be a generous gesture by SIG conveners as it will involve them in extra work and time corresponding back and forth with the authors and getting a final form of the abstract agreed with them to submit. It would also increase the time between submission of abstracts and the meeting by 3–4 weeks, which meeting participants generally find inconvenient. This issue will be considered by Council who will report back on it to the next AGM.

There were also three proposals put forward by Roger Thomas, who can always be relied upon to enliven the meeting. One related to registration fees for meetings, but as this had already been discussed and passed under the Council resolution, it did not require a re-iteration. His second proposal was that the abstract of demonstrations at society meetings should be published in *The Journal of Physiology*. There was support for making more of demonstrations and highlighting them; however, what is published in the journal is a matter for its Editorial Board and had to be raised with them. Roger's final motion was about the publication of abstracts and the provision of abstract books that combined both congratulating and admonishing those responsible. Roger decided to withdraw this motion at the last minute, so there was no opportunity for Members to respond to it.

Mike Collis

2009 membership subscriptions

The Society is pleased to announce that there will be no changes to the cost of membership subscriptions for 2009.

Subscription fees will remain as outlined in the table below.

Ordinary Members are also eligible to receive a discount on hard-copy subscriptions to The Society's publications, *The Journal of Physiology* and *Experimental Physiology*. For 2009, the discount will be 60% of the European retail price as follows:

The Journal of Physiology £130
Experimental Physiology £39

Membership category	Subscription fee if paying by direct debit	Subscription fee for non-direct debit payments
Ordinary Member	**£80**	£90
Affiliate		
UK and RoI	**£20**	£25
Online only	**£15**	£20
Europe	**-**	£40
Rest of world	**-**	£45
Associate	**£40**	£45
School and College Associate	**£15**	**£15**
Undergraduate Associate		
Individual	**£15**	**£15**
Institutional (>5 members)	**£10**	**£10**

Proceedings of Society meetings

Does anyone have unwanted print copies of J Physiol volumes containing the Proceedings of Society meetings between 1999 and 2000 (volumes 517P to 533P)? The copies are needed for a project to scan the Proceedings between 1998 and 2000 when there is a gap in the online record. The volumes will be destroyed during scanning. Please contact Carol Huxley (chuxley@physoc.org).

J Murdoch Ritchie

The Society notes with regret the death of J Murdoch Ritchie, a Member of The Society since 1951.

From the archives … 'Hairs' apparent! This recently discovered slide shows four Members of The Physiological Society in their prime. In the 1970s, this lab in Leicester University was at the cutting edge of cardiac cell physiology, if not at the cutting edge of the barber's scissors! The picture shows Reg Chapman, now sadly deceased, with his PhD students, post-doc and departmental lab technicians. On the back row, from left to right, we see: David Ellis (Edinburgh), Chris Fry (past Society Chairman, Surrey), David Miller (Glasgow) and Reg Chapman; the identities of the women in the front row remain unknown! In 1971 there were about 1000 Members of The Physiological Society; today the number of Members exceeds 2600. With the growing popularity of digital photography, we can look forward to some equally amusing historic images in 30 years time …

Discover Biology

All events free*

Pond dipping, mature mega plants, biodiversity today and tomorrow

11:00–15:30 Saturday 6 September
Field trip for all at the Ness Botanical Gardens

Schools' Programme: Years 9–13 Biology Road Show

Bird flu *Tuesday 9 September*
Brain waves *Wednesday 10 September*
Stem cells *Thursday 11 September*
Events from 09:30, 11:30 & 14:30 at Liverpool University

Obesity: Fat of the land, or land of the fat?

09:15–13:00 Monday 8 September
Science for all at the Barkla Lecture Theatre, Chadwick Building, Liverpool University

Cystic Fibrosis: Better understanding, better lives

09:30–11:30 Tuesday 9 September
Science for all at the Proudman Lecture Theatre 027, Liverpool University

Plant power: Fuel for the future or a load of hot air?

19:00–21:30 Wednesday 10 September
Science for all at The Piazza, Metropolitan Cathedral

* Except for the Ness Botanical Gardens event which costs £3.
All events (including free events) must be booked in advance.

Book Schools' Programme: www.merseysidesetpoint.org.uk
or phone: 0151 231 2400

Book Events: www.the-ba.net/festivalofscience
or phone: 020 7019 4947

Sponsored by: BIOSCIENCES FEDERATION **www.bsf.ac.uk**

Incorporating: Biochemical Society, Society for Endocrinology, Nutrition Society, The Physiological Society, British Ecological Society, Society for Experimental Biology, Society for General Microbiology, Nottingham Trent University, Southampton University

Mouseystan

How well meaning scientists, the British Government and animal welfare legislation turns transgenic mice into terrorists

Earlier this week I was gravely wounded in an unprovoked and frenzied terrorist attack – a transgenic mouse savagely nibbled my index finger. I was seriously injured, mentally traumatised and needed a plaster. I originally thought that my injury was simply due to a random attempt at assassination by a mentally disturbed mouse acting alone. Then I examined the accident book and realised that in a 1 week period seven other researchers had been critically injured in similar unprovoked attacks. They needed plasters too.

I don't have the kind of fragmented and disordered borderline personality that is attracted to conspiracy theories (actually I do), but after several minutes of detailed investigation I have uncovered a sinister conspiracy. In the following groundbreaking study I can demonstrate how well meaning scientists, animal welfare legislation and the British Government have conspired to create a climate where naïve and innocent mice are alienated from mainstream society, radicalised and transformed into 'murine jihadists' with a messianic hatred of anybody in a white coat.

I have discovered that this transformation typically follows a 7-stage developmental and consolidation process.

Stage 1. Genetic susceptibility
During development mouse has his genome sequenced and interfered with, this induces epigenetic modifications to genes that control behaviour. Mouse is therefore predisposed to develop a range of behavioural problems including hyperactivity, oppositional conduct and attention deficit disorders. Mouse enters his early childhood with 'a volatile personality'.

Stage 2. Early childhood
Overprotective and anxious middle class vegetarians then blame scientists for the increasing incidence of behavioural problems in mice by attributing behavioural problems to the incorporation of E numbers in standard non-organic mouse chow by evil multinational companies. Neonatal mouse repeatedly hears this and grows up believing that he is not responsible for his own behaviour and that capitalism is evil.

Stage 3. Adolescent influences
In early adolescence a transgenic mouse overhears the Home Office Inspector, militant vegetarians and associated social misfits discuss him in great detail. Mouse then realises that there is a huge range of animal welfare legislation pandering to his every whim and that 'scientists are evil'.

Stage 4. Mouse has transgenic philosophical epiphany
Transgenic mouse then believes that he is 'special' and develops a sense of entitlement. Mouse then behaves in an overtly aggressive and arrogant manner and expects special treatment from society.

Stage 5. An aggressive and arrogant mouse suffers increasing social isolation and stress
Transgenic mouse then becomes disaffected when his sense of entitlement is ignored and suffers increasing mood swings.

Stage 6. A stressed mouse becomes an easy target for dangerous propaganda
A stressed transgenic mouse then sneaks out of his cage at night and uses the designated records computer that the Home Office has ordered you to install to observe inappropriate 'murine jihadist' web sites. These sites show mice being ill treated in Cheznia, Iraq and a small town called Hamlin in Germany. Mouse also communicates with other radicalised mice in volatile areas of the Afghan border and receives military training by e-mail.

Stage 7. Mouse then develops a messianic complex
An increasingly obsessed, marginalised and embittered mouse develops a messianic hatred of scientists and launches a deranged suicide attack on an innocent scientist's finger.

Without specialist training, spotting an individual mouse with a messianic hatred of scientists is not easy. Personally, I have never trusted the C57, black 6 strain. All that inbreeding is bound to make you a bit strange (have you ever seen the film *Deliverance*). The way they sit in the corner of the cage, looking at you with those dark beady eyes and squeaking in their own language. You never know what's going on in their little devious minds do you? I never had that problem when I worked with Sprague-Dawley rats - cute little rat, nice white fur and pink eyes. You could understand it when they bit you, I blamed the parents.

As a result of these ideologically inspired 'savage nibbling incidents' our department has taken a number of unprecedented steps to increase security around our staff. These include the disconnection of internet links out of office hours and the banning of the import of any transgenic mice from politically unstable areas of the world. We have also distributed to all staff the publication *Murine intelligence gathering, restraint and interrogation techniques for the 21st century* published by Fort Langley Press, West Virginia. Personally as a physiologist with an unspecified personality disorder, I feel almost erotically drawn to the beautifully written section in chapter 6 entitled *Waterboarding in the mouse* (*Mus domestica*). A minor physiological stressor, maybe? Animal torture, certainly not!

Keith Cormorant would like to state that the mouse that bit him is still alive, in an anonymous mouse house in Uzbekistan.

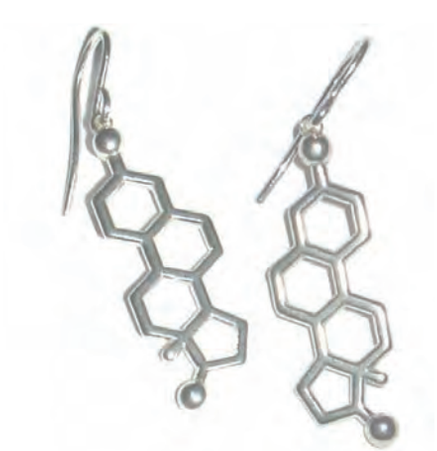
The other side to scientists

Having always been torn between the arts and science, but opting for science as a means of making an honest living, I retain an avid interest in arts and crafts. Some people are surprised to learn that scientists can be artistic, but if you ask around I'm sure you will discover that many of your colleagues harbour secret abilities such as playing a musical instrument, drawing, metal-smithing or photography. Just think of Leonardo da Vinci, and a few other famous artistic scientists might spring to mind. Now, we're not all able to paint a Mona Lisa or invent a flying machine, but I am always delighted to discover fellow scientists who, like me, feel the need to create and so am pleased to introduce you to the Mad Scientists of Etsy. Etsy is an online marketplace for all things handmade and hosted in the US, but sellers and buyers are located worldwide. Many sellers are keen recyclers and promote green issues. The Mad Scientists team is the brainchild of bijoutery, also known as Jennifer Earles – an American graduate student of geoscience and a jewellery maker. Jennifer started the group to bring together artisans, who are also scientists, to exchange ideas, promote each other's shops and generally support each other. The Mad Scientists are a varied bunch – biochemists, neuroscientists, geo-physicists, environmental scientists, and at least one physiologist!

Now I don't know about you, but I hate shopping – the crowds, gormless sales assistants and having to carry my purchases home in the rain – so internet shopping has been my saviour and I'll take you on a quick tour of what's on offer from the laboratories of the Mad Scientists of Etsy. Most sellers gift-wrap their products and many will create customised or personalised items. The url for any shop can be obtained by adding etsy.com after the username, e.g. bijoutery.etsy.com. Etsy also has categories for browsing and a search engine to find that perfect item – type 'msoeteam' into the search bar.

If you need a special gift for a wife, fiancée, girlfriend or partner then look no further than the many jewellery shops, which include bijoutery for pearl and gemstone jewellery, beautiful fine silver biology-themed jewellery from eggtoothoriginals, all kinds of molecules in silver from molecularmuse (yes, she's a bio-chemist) or make a beeline for thebline, who teaches chemistry.

Rockstar lab coat from buffalonerdproject (top); Huge heart plushie from FurWillFly (above); Estrogen molecule earrings from molecularmuse (below). A full list of shops with links to the Etsy team is available at http://team.etsy.com/viewteam.php?id=265.



Know someone with children? Then you really must check out UK seller FurWillFly's hilarious biology-based creations in fleece and felt – from Ig the antibody to the Insiders – plushies with large anatomical features on their outside. Still on the felt theme, clairepayne makes iPod cases and brooches from her 'lab' in Birmingham and environmental toxicologist, eikumpel makes brightly-coloured plushies in Yeovil. If you're having a party – take a look at momentsbymartha's wine glass charms and avoid a mix up with which glass belongs to whom. Still in the UK we have hand-embroidered bookmarks, wallets etc from katecronin72.

Now for a quick hop over the pond. Check out soap for handmade soaps for all genders and skin types. You can get animal-shaped cushions from minouette and stained glass creations from Quingawaga in Canada, really cute tote bags from pre-med student itsybitsyindustries, soy candles from fish ecologist, inseinecreations. Now this is a personal favourite as it's such fun – an embellished 'rockstar' lab coat from biology lab technician buffalonerdproject. She's got some seriously nerdy ties too. Feeling the chill of a British winter? Visit a pharmacist also known as Happiknits and she'll sort you out with a shrug or scarf. Or how about a card that grows: a columbine seed-embedded card from primatologist, recyclediideas. If safetythird sounds like something in your lab, check out her shop for some really fun T-shirts. Finally, to talented artist and biochemist, jvdarcy, who works with many media and photographer kwinkelerphotos for great biological images.

This is a just a flavour of what scientists can do with art. Prices are currently in US dollars but eventually a currency converter will be made available and secure payment can be made through PayPal. Buying handmade from Etsy supports the seller directly and cuts out the middleman. Furthermore, there's a very personal touch to handmade goods that are made with care and enthusiasm that is rather refreshing in today's world of mass-produced products.

Patricia de Winter

Units, symbols, and abbreviations

A guide for authors and editors in medicine and related sciences
By Denis N Baron and H McKenzie Clarke. RSM Press, 2008.
56 pp, £7.95 (paperback)
ISBN 978-1-85315-624-3

This very concise little book is aimed primarily at clinicians, but there is plenty in it that is useful for basic scientists and allied health professionals. It has four chapters, the first two of which deal with SI units, the principles underpinning the system and lists of the base and derived units that are most commonly used in medicine. The third chapter very briefly outlines the citing of references and the fourth is a comprehensive list of proof correction marks used in editing.

The SI system is effectively explained in a concise and factual style in the first half of this book. Base units are defined by their physical characteristics and selected derived units are listed in terms of both other derived units and of base units. The correct use of prefixes and unit formation is explained. Commonly used abbreviations (with some bias towards those commonly used in medicine) are listed and the preferred terms are specified, as well as those that should be avoided. Non-SI units that are accepted for use with SI because their usage has become so entrenched in human culture are also mentioned. In brief, the first two chapters do a very good job of summarising the rather hefty document produced by the Bureau Internationale des Poids et Mesures.

The third chapter deals with referencing and at only just over four sides long, it is very brief indeed. Procedures for referencing journals, books, theses and digital object identifiers are outlined, but the only two referencing systems quoted are Harvard and Vancouver. Although these are the two systems that clinicians and basic scientists are most likely to use, the title of this book does include allied health professionals, and these are somewhat ignored in this chapter. For example, clinical psychologists favour the American Psychological Association system. This is the only chapter that I felt could do with being expanded a little. The final chapter is in effect a useful tabulation of the most commonly used proof correction marks. It lists instructions, marks in text and marks in the margin.

This little paperback is remarkably informative for its size. It is a quick reference source for anyone writing theses or papers and is very reasonably priced. It is small and light enough for the geeks amongst us (myself included) to carry it around in a bag or a large pocket, in anticipation of being asked to convert mmHg to pascal in a literary emergency.

Patricia de Winter

NOTICEBOARD

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

SECC, Glasgow, UK
SEBatGlasgow2009 (SEB Annual Main Meeting 2009)
28 June–1 July 2009
www.sebiology.org/meetings

Physiological Society Meetings

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

2008

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
http://www.beijingphys2008.org

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 crosstalk and integration*

2009

King's College London, UK (1–3 April)
Human & Exercise PhysiologyThemed Meeting

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

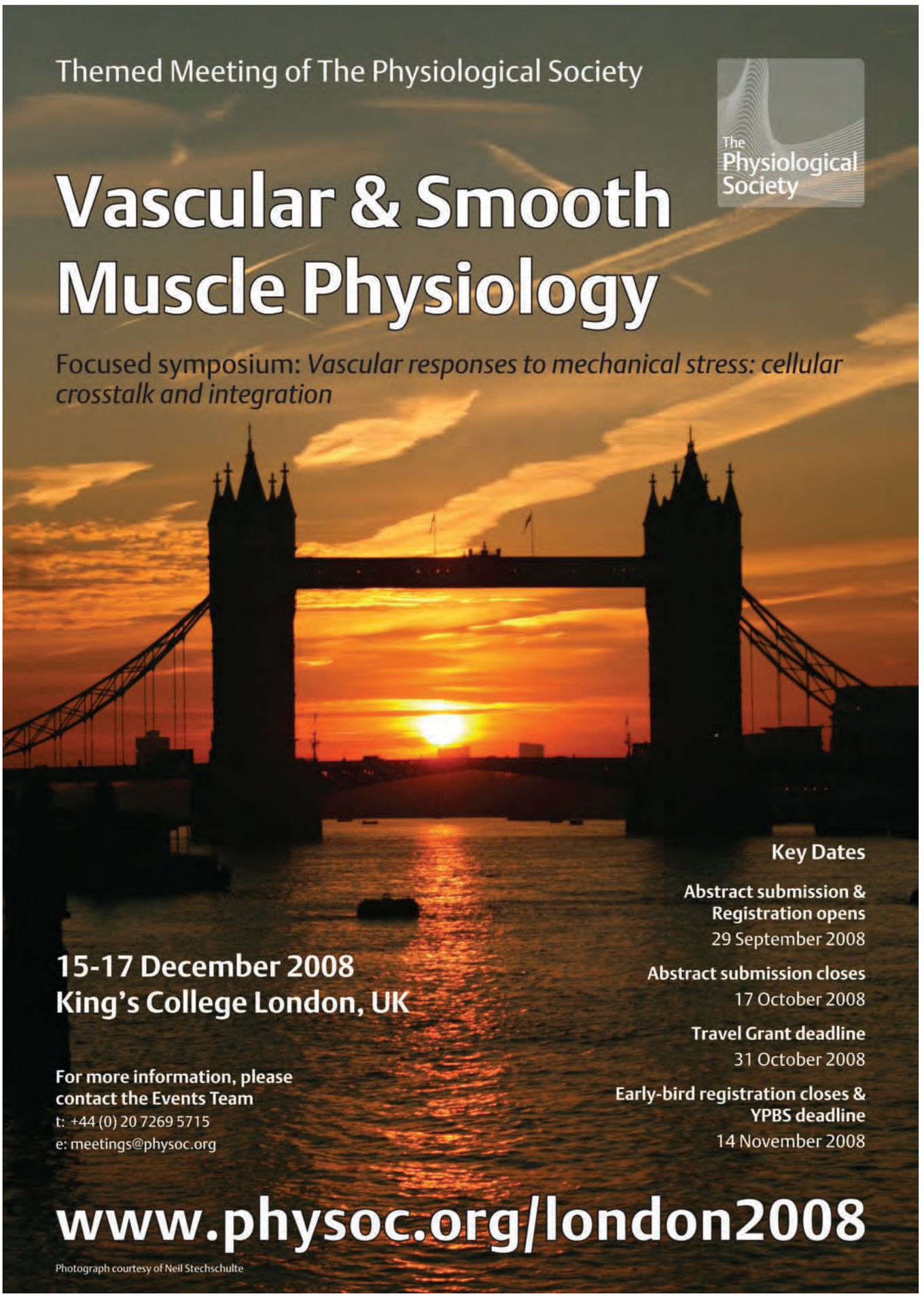
University of Newcastle, UK (September)
Epithelia & Membrane Transport Themed Meeting

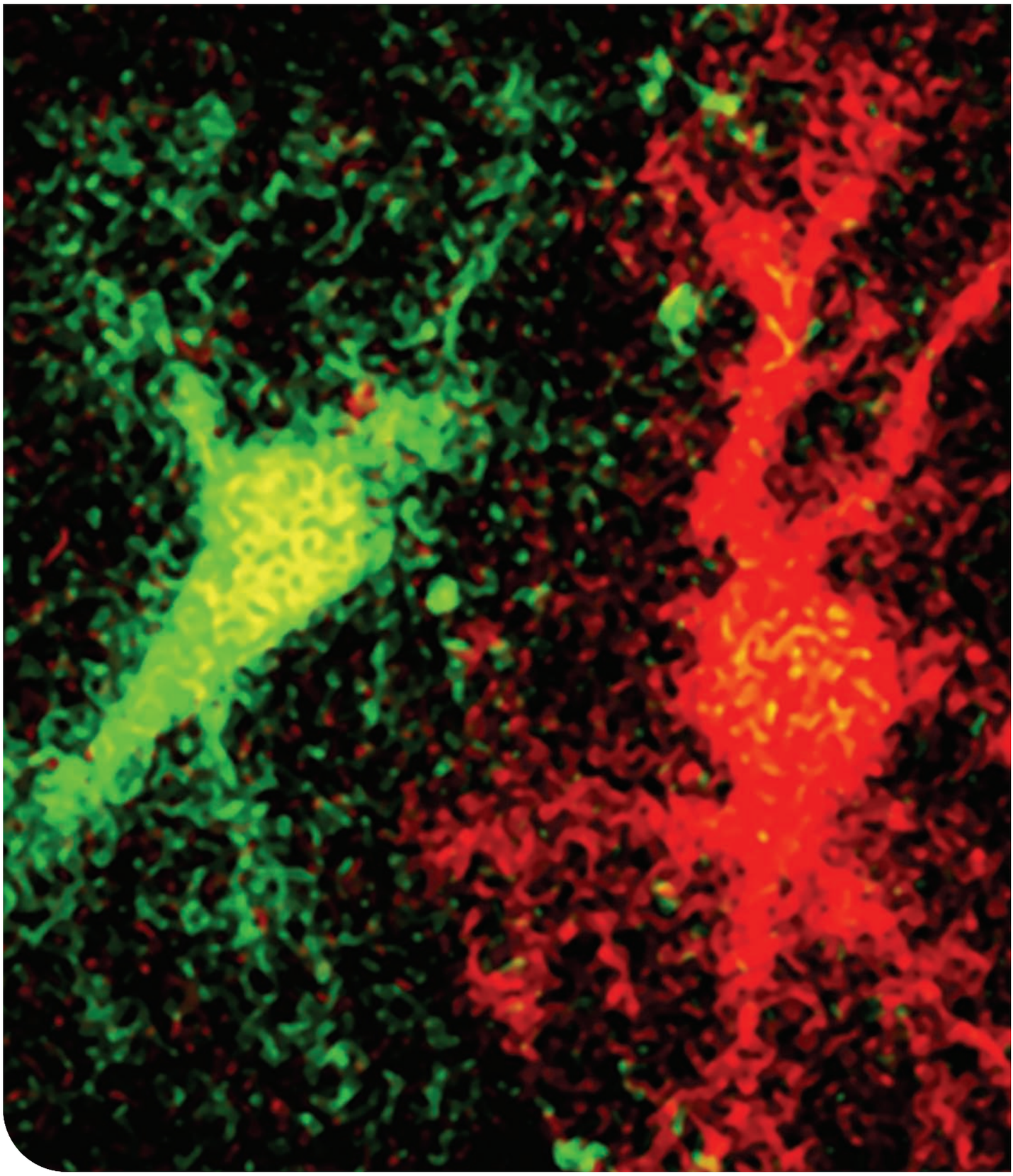
Woods Hole, MA, USA (September)
Joint International Meeting of The Physiological Society with the Society of General Physiologists on *Basic biology and disease of muscle*

Cardiff University, UK (14–16 December)
Cellular & Integrative Neuroscience Themed Meeting

2010

University of Manchester, UK (July)
Main Annual Meeting


Themed Meeting of The Physiological Society
The Physiological Society
Vascular & Smooth Muscle Physiology
Focused symposium: Vascular responses to mechanical stress: cellular crosstalk and integration
Key Dates
Abstract submission & Registration opens
29 September 2008
Abstract submission closes
17 October 2008
Travel Grant deadline
31 October 2008
Early-bird registration closes & YPBS deadline
14 November 2008
15-17 December 2008
King's College London, UK
For more information, please contact the Events Team
t: +44 (0) 20 7269 5715
e: meetings@physoc.org
www.physoc.org/london2008
Photograph courtesy of Neil Stechschulte



Patch-filled astrocytes with two different coloured fluorescent dyes (Fiacco & Agulhon, p.18).

A publication of The Physiological Society
www.physoc.org