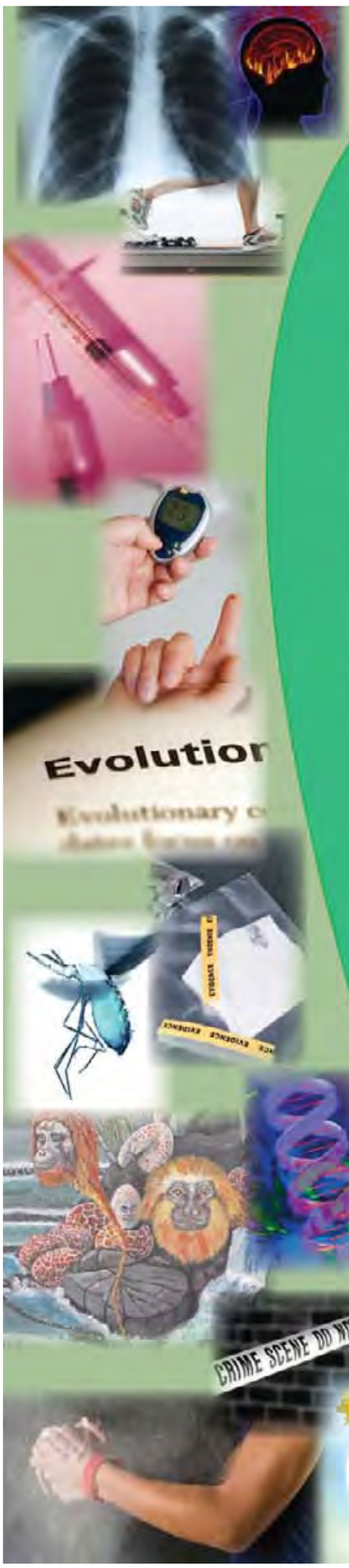
PHYSIOLOGY NEWS

winter 2008 | number 73

The HoD delusion
A Christmas party trick with an intriguing physiology
A new organisation for the biosciences
Ion channel techniques in Shanghai



BIOLOGY IN THE REAL WORLD: BRINGING THE CURRICULUM TO LIFE

9.30 ☛ *What is diabetes?*
Dr Aileen King

10.15 ☛ *Why do we need a new vaccine for tuberculosis?*
Dr Helen Fletcher

11.30 ☛ *Drugs of abuse: psychoactive & performance enhancing drugs*
Dr Emma Robinson

12.15 ☛ *What would a monkey do?*
Dr Lynda Boothroyd

14.00 ☛ *Health impacts of climate change*
Dr Hugh Montgomery

14.45 ☛ *Flowers, forensics & pharmaceuticals*
Prof Monique Simmonds

16.00 ☛ *Bringing the real world into the classroom*
Dr Jeremy Airey

Venue: Lecture Theatre 109
Palmer Building
The University of Reading
On: Friday 9 January 2009 9.30–16.45

Sponsored by members of NUCLEUS: a group of learned societies & similar not for profit organisations.

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

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The Physiological Society
Advancing the science of life

Front cover image by Brian Robertson (from *Latest advances in ion channel techniques*, p. 5)

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

Membership applications
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:
http://www.physoc.org/membership

Is your membership information correct?
Please check and update your details at www.physoc.org, under 'My Physoc Profile'.

Physiology News

Deadlines

Letters and articles and all other contributions for inclusion in the Spring 2009 issue, No. 74, should reach the Publications Office (lrimmer@physoc.org) by **23 January 2009**. Short news items and letters are encouraged, and can usually be included as late copy if space permits.

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

***Physiology News* online**
Physiology News online:
http://www.physoc.org

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 Winter 2008 *Physiology News*.

As I have written before, the keys to making a magazine worth reading seem to me to be 'interesting and relevant', 'variety', and 'good writing'. Looking at the first two, it is to our good fortune that physiology is an intrinsically 'broad church' subject, taking in everything from genomics to behaviour. Just to take three adjacent *Science News and Views* articles from this issue for an example, we have a levitating-arm party trick that illustrates interesting principles of human motor feedback control (p. 12); ammonium in the bee retina and its possible relevance to mammalian brain (p. 15); and the sensing of the fullness of the bladder (p. 18). I would call that simultaneously relevant *and* varied.

Variety is also why we aim to produce a wide range of feature articles. This time we have a handy guide to how to be a Head of Department (p. 7), as well as features covering meetings, education, news both national and international, policy, history and humour.

Surveys of readers of professional magazines often show that obituaries are among the most read bits. An obituary can simply give you details of a person's professional history and achievements, but better ones give you that information in the context of their life and character. The very best obituaries not only do this, but give you a real sense of the person. The wonderful appreciations of J Murdoch Ritchie on p . 49–51 fall into this latter category.

Finally, this issue marks a couple of anniversaries for me personally. It is 10 years exactly since I first got involved with *Physiology News*, and almost exactly 5 years since I took over as Editor; my first editorial meeting 'in the chair' was December 2003. I hope we have kept you informed and entertained this last decade, and that we can continue to do so in the future.

Austin Elliott
Editor

It's not all doom and gloom – the recession and research funding

Pessimists will thrive on recent headlines screaming out about the economic downturn; I have heard comments that research funding will be slashed, but how much of this is fact and how much is scare-mongering?

Firstly, a definition of 'recession' would not go amiss. The standard press definition is at least two quarters of zero or negative growth (gross domestic product, GDP). Most economists think this definition flawed and prefer to use additional indicators such as employment figures, real incomes and production. GDP decreased by 0.5% in the third quarter of 2008, compared with a 0.0% movement the previous quarter*. So, if we're not officially in recession yet, we likely will be by the time this issue goes to print.

The UK has endured three recessions in the past four decades (Fig.1). Not all sectors of the economy are negatively affected to the same extent; some industries are traditionally 'recession-proof' - for example, education, health and the emergency services. Numbers employed in education, health and public administration remained steady during the recession of 1990–91, whereas 315 000 jobs were lost in distribution, hotels and restaurants, a recession-sensitive sector*. This is comforting for those of us employed to teach but is research recession-proof?

One way to answer this question is to examine historical figures and use these to predict what might happen during another recession. UK non-commercial science research is funded mainly by research councils and charities. The income of both might be considered sensitive to economic conditions: simplistically, the Government relies on tax revenue and charities rely on investment income and on corporate and individual donors. Reduced income to these funders might be predicted to impact negatively upon how much they can award to research, but is there any evidence that this occurs?

Government spending on science, engineering and technology (SET) has increased since 1986, though the

*http://www.statistics.gov.uk

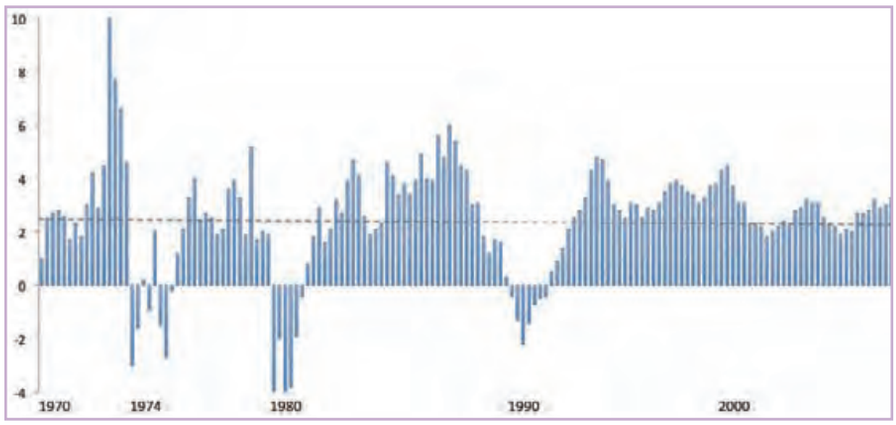


Figure 1. UK gross domestic product (% growth), quarter on quarter, 1970–2007. Dashed line: average GDP since 1955 (source: Office for National Statistics).

1994–95 increase may have been partly influenced by overheads on research council grants and the post-2005 increase is likely to have been inflated by full economic costing (Fig.2). The BBSRC was created after the 1990–92 recession, but the MRC, in existence since 1913, received above-inflation funding increases during the last recession. The huge increase in total SET spending from 2000 came mainly from increased funding to the Office of Science and Technology and coincides with Lord Sainsbury's term as Science Minister.

This leads us nicely on to funding from charities. There is good news for neuroscientists; in 2005 the aforementioned peer, then 65, announced his ambition to give away £1 billion to his trust, the Gatsby Charitable Foundation, during his lifetime. With regard to other charitable organisations, the CEO of the BHF is not anticipating a major drop in budget next year (personal communication from Jeremy Pearson) and recently Harpal Kumar, Chief Executive of CR-UK refuted media claims that a fall in donations will leave projects short of funds for up to 5 years, calling such statements 'incorrect and grossly misleading'. The key player is the world's largest medical charity, the Wellcome Trust. With a well-diversified investment portfolio and endowment of £15 billion, I suspect it can weather the current storm. Smaller charities may feel the pinch to a greater degree but, although this may affect individual researchers, it is unlikely to have a major impact on funding as a whole. Available evidence thus suggests that research funding is reasonably insulated from the vagaries of the economy. So it seems that it's not all doom and gloom.

Patricia de Winter

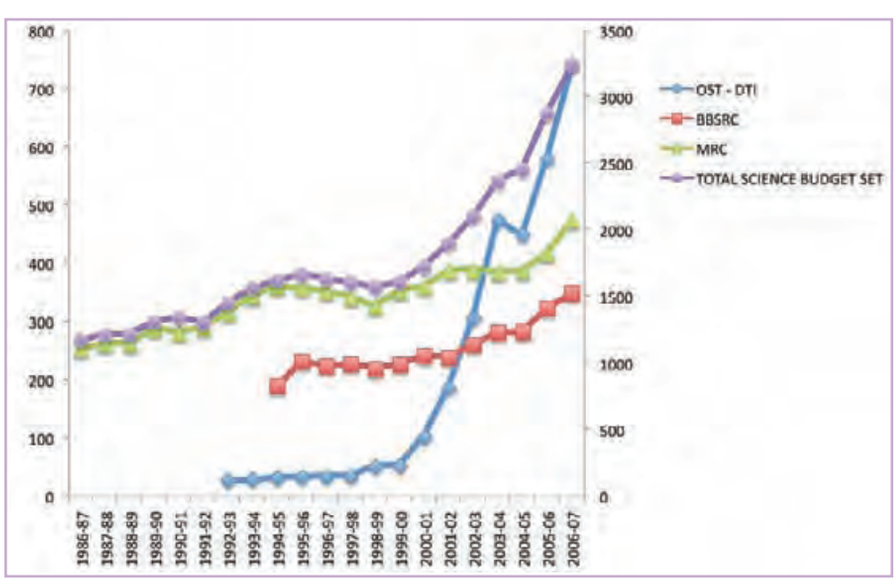


Figure 2. UK Government spending (£ million) on selected biological research councils and the Office of Science & Technology (left axis) and total science budget (right axis) (source: Department for Business, Enterprise and Regulatory Reform [BERR]).

Vascular and smooth muscle physiology Themed Meeting at King's College London

King's College London will host the third Physiological Society Themed Meeting from Monday 15 to Wednesday 17 December at their Guy's Hospital Campus, which is located close to the River Thames at London Bridge (aerial image above).

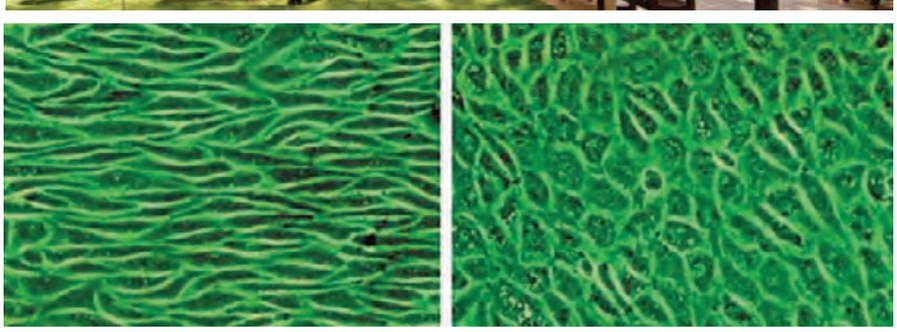
Cardiovascular disease is now recognised as a major cause of death and disability in the developed world and arises from the adverse interaction of disease risk factors, such as high cholesterol, with the functions of the blood vessel wall, leading to high blood pressure, stroke, angina and heart attacks. Heart disease can often be prevented by lifestyle changes which have a major effect on reducing the risk of developing symptoms. This has resulted in a rise in basic and clinical cardiovascular research over the past two decades as well as public education and interest in this field.

The biophysical interactions between blood flow through arteries and alterations in the function of vascular cells remain a central focus to better understand the mechanisms involved in vascular diseases. This field has recently gained wide interest and this meeting will feature a timely symposium on *Vascular responses to mechanical stress: cellular crosstalk and integration*. A number of world leaders in this field have been invited to speak at the meeting, including Shu Chien (University of California, USA), Stephanie Lehoux (McGill University, Canada) and Peter Davies (University of Pennsylvania, USA). The full invited panel of speakers is listed on the inside back cover. This forum truly represents a unique opportunity for the integrated understanding of both physical forces and their biological consequences within blood vessels which contribute to normal cardiovascular physiology and disease progression.

The Christmas season in central London will provide delegates with an opportunity to sample the festive delights of Borough Market and the South Bank, located in the immediate vicinity of the meeting venue, while transport links, restaurants and accommodation in the local area are excellent.

Abstract submissions for this meeting will be considered on all aspects of vascular and smooth muscle physiology and online registration for the meeting closes on Monday 1 December, so there is still ample time to participate in this exciting meeting. We warmly welcome you to attend and look forward to seeing many of you in December. For full details go to http://www.physoc.org/london2008

Richard Siow
Maggie Brown
London 2008 Meeting Organisers
Microvascular & Endothelial Physiology SIG Convenors



Latest advances in ion channel techniques

The Society's International Workshop in Shanghai gave students the opportunity to appreciate state-of-the-art techniques used in a range of cell types

I have seen places that were, no doubt, as busy and as thickly populous as the Chinese city in Shanghai, but none that so overwhelmingly impressed me with its business and populousness. In no city, West or East, have I ever had such an impression of dense, rank richly clotted life .... it is Life itself (**Aldous Huxley's diary, 1926).**

From 12–16 September a Physiological Society International Workshop, *Latest Advances in ion channels techniques applied to physiological problems*, took place in Shanghai. Our host was Mu-ming Poo, Director of the Shanghai Institute of Neuroscience (ION), one of the most prestigious neuroscience research institutes in the world. Though founded less than a decade ago, ION already has 21 separate group leaders and will have 30 laboratories by 2010. Each of these labs regularly publishes at the very highest levels in various disciplines of neuroscience.

The major aim of the workshop was to provide PhD students (and some early postdocs), mainly from the Far East, with an opportunity to gain an appreciation of state-of-the-art techniques being employed in the study of ion channels in a range of cell types. Students applied from all over the globe, and successful candidates came from as far afield as Brazil and Australia, Israel, the Ukraine and Romania, with some from the UK and many from China. We had 16 speakers, with the European contingent originating from Edinburgh to Belfast to London via Cardiff, Manchester and Leeds. Maintaining the international flavour, we had five speakers working in China, with a further three being Chinese-born investigators in the UK. Sonja Stoelzle came from Nanion GmbH (Germany) to present on automated patch clamp devices and demonstrate their Portapatch device, which does away with the need for large and expensive conventional electrophysiology rigs. The speakers work on ion channels in a huge variety of tissues, from brain slices to bladder, from sperm to TIRF images of synaptic vesicles in neuronal processes, from megachannels derived from isolated heart muscle to animals *in vivo*. The variety of lectures revealed to the audience just how diverse ion channel research can be, and how different tools can be used to ask questions about the physiology or pathophysiology of a particular cell, tissue or organ. Each speaker gave a research talk introducing their particular techniques in the context of their own research problems, be this LTP in brain slices, drug discovery, or how permeation occurs in calcium release channels in the heart. Following each talk there were a couple of small group tutorials, allowing students to come up with their own questions and allowing lecturers to explain technical aspects in more detail.

Aside from all this high-powered and wide-ranging science, there were opportunities for social events, with a welcome banquet and an

absolutely spectacular farewell meal in a new and chic restaurant by the river in Pudong; this was followed by a river cruise, where the full splendour of Shanghai was on display. On the Bund bank, the status architecture of commerce and banking power from the 1930s, but on the ever-changing Pudong side, the breathtaking skyline comprised of some of the confident marvels of 21st century building technology –the movie set of *Blade Runner* now.

The cuisine in Shanghai is amazing in terms of its quality and variety, and our Chinese hosts made a considerable fuss of us, for which we are extremely grateful. There was only one unfortunate incident, in which one of our number decided to sample some authentic street food in a crowded road with some major hospitals and many busy little food stalls and booths. It wasn't clear whether the food sellers were there to service the large hospitals or *vice versa*, until a few hours later, when the full and impressive hydraulic power of the human GI tract became evident, with the poor victim assuming a 'Zen archer' like total physical union with the hotel plumbing.

All of the students presented excellent posters, which were on display each evening. The speakers judged and scored these posters and questioned presenters on their work and allied areas. Amazon gift vouchers were awarded for the top four posters. Pan-Li Zuo (Peking University, China) won the Wiley-Blackwell Prize for Most Innovative Physiology, whilst three others (Shai Berlin (Tel-Aviv University, Israel), Balazs Horvath (University of Debrecen, Hungary) and Bo-Yi Liu (Hebei Medical University, China) also received prizes.

Whilst the workshop was a success, there were some lessons to be learned that could be used to improve future international workshops. Some of the students felt that more hands on experience would have been better, though this can be difficult to organise in a faraway location. Is 'workshop' the right name? One disappointment was the number of students who accepted places but couldn't make it, and there was no chance to replace them at short notice. Sadly, a few of our attendees were more attracted to tours than talks. Overall, however, the overwhelming impression was of an invaluable opportunity to explore new avenues in physiological research and collaboration, and this is one of the aims of The Society. For my own part, I am grateful to everyone who attended, to all the speakers for doing an excellent job, to Mu-ming Poo for allowing us to use his excellent staff, students and facilities, to my co-organisers Ian McFadzean, Weifang Rong and Tian-Le Xu, to David Bennett in The Society's London office, to Nanion and Wiley-Blackwell for sponsorship, but most of all to Yi-Xi Gu, ION's, Scientific Exchange Programs Officer who was the not only the most marvellous organiser and fixer, but had a never ending supply of good humour and care. Thank you all.

Iain James (Almac, Belfast) (*left*), Alan Williams (Cardiff) and Ian McFadzean (King's College) enjoying the river cruise.

Brian Robertson
The Journal of Physiology and
Edinburgh College of Art

The HoD delusion

A Head of Department writes

It is frequently said, though I forget who started it, that managing academics is like herding cats.

My experience, as both cat owner and Head of Department (HoD), suggests that this is grossly unfair to cats; our feline friends tend not to discuss their destination at length, let alone all the ins and outs of if, why, and how they want to go there; nor do they resist change with nearly as much enthusiasm as academics.

Over several years I have realized that becoming a HoD, rather than cat-herding, is more like becoming a parent – for the following three reasons in particular. First, you take it on in addition to your other jobs; second, nothing really prepares you for the reality; and third, you undertake its major responsibilities and possible consequences with little – if any – appropriate training. I'm sure there are other reasons too – note that I have studiously avoided the various possible scatological parenting-HoD analogies that spring to mind on bad days.

For my own amusement I have therefore compiled the following *10 commandments* for anyone entering upon HoD-ship. Although I can't say that I have succeeded in obeying all of them, they seem important (at least to me); others might like to amuse themselves by compiling their own.

1. *Know your objective(s) and act accordingly*. When I was first asked to be HoD, I felt the normal mixture of fear, trepidation and received flattery. Speaking to a friend at a meeting, he told me 'only do it if you know what you want to achieve and what needs to be done to get there'. Several years on, this still seems excellent advice. The role of HoD is only worth doing if you can see what needs doing (and why) to develop the department. The objective may be the formation of a research institute, or a streamlined department that is excellent in teaching and research. Whatever the vision, it is vital that the objective, and the strategy for achieving it, are clear to everybody in the department, that they sign up to it, and that every decision should help achieve it. A decision may be large and far-reaching; small, if no large opportunity presents itself; or no decision, which can be valid in some circumstances. All choices made, however, should help achieve the objective in an organised and transparent manner; opaque management and crisis management are the best possible ways, bar none, to demoralise a department.

2. *Lead from the front*. University staff are under increasing pressure to do all sorts of things: to deliver high quality teaching to increasing numbers of fee-paying students, to produce high quality research for the RAE, to deal with ever increasing amounts of paperwork to fulfil legal and university obligations, and to undertake many other activities, such as public engagement. As HoD you have the (very) dubious pleasure of distributing such responsibilities fairly. However, if you are asking more and more of colleagues, it is only fair that you should also contribute to these activities yourself – to an extent that is, at the very least, commensurate with what is being asked of others and with your other responsibilities. This also has the advantage of providing a reality check by keeping you in touch with things 'on the ground'. It is also important to lead and manage actively to make things happen, and to ensure they are done efficiently, effectively and fairly, not just shuffle paper. However, this doesn't mean that you have to do everything yourself! There are probably not enough hours in the day for the amount of paperwork that your institution is capable of throwing at you, which is where the 3rd commandment comes in:

3. *Manage your time carefully*. When faced with a new task, you must decide: Is it urgent? Is it important? (and to whom – as a colleague expressed it, 'a crisis on their side does not represent an emergency on mine'). Can it be binned? Can it be delegated? Delegation is important, not only for your sanity, but also because other people have, or can develop, expertise that means that they can do it better than you. This involves them in running the department as well as developing their responsibilities and hence career progression. The degree of delegation will depend on the person, but it does *not* mean 'do it for me, exactly the way I would do it'. At all costs you must avoid micro-

management – if you don't trust somebody to do the job, you shouldn't have delegated it to them. Next question – if you must do something yourself, how perfect does it need to be? The more you work on something, the less improvement you achieve per unit time, so you need to decide where the cut-off is for each job. Finally, keep a diary: put in meetings, deadlines, times to do things well before the deadline to allow for slippage, reserve time for research ... but you know this already otherwise you wouldn't be heading for HoDship.

4. *Be accessible.* As HoD it is important to listen to the comments, complaints, suggestions and requests of your colleagues if you are to have your finger on the pulse of the department. There are many different ways to achieve this, from regular attendance in the coffee room, to walking the corridors, to having an open door policy for all members of staff. You are working with everybody in your department towards a common goal, which can only be achieved by inclusivity and good two-way communication. Personally, though, I have always found it helpful to listen more than I talk – I learn a lot more that way.

5. *Don't judge or act until you have heard both sides of the story* (if there is more than one). If a request or complaint seems unreasonable, try and put yourself (metaphorically) in the other person's shoes. Things frequently look very different (and more reasonable) when seen from the other person's point of view; what may appear trivial to you may not be to them. If more than one person is involved, don't jump to conclusions based on only one side of the argument (and don't respond only to your most vocal colleagues). Listen to all those involved and draw your own conclusions, after taking time to find further information if necessary.

6. *Say 'yes' when you can, but learn to say 'no' when necessary.* More than 90% of the requests I have received as HoD are entirely reasonable when seen from the point of view of the person making the request, and the vast majority will help the department or individual (who will normally know best what would be helpful for them) in some way. Saying yes is, therefore, frequently the best response.

However (and it is a big however), there may be other factors, or repercussions that the individual is not aware of, that make it necessary to turn down a request. If this is the case, it is important to do so *and* to explain why – in person if possible, not by e-mail. Most people, if given an explanation, will accept the necessity and see the reason for your decision, even if you don't leave them with a spring in their step.

7. *Do what you believe to be right and fair.* Take soundings and advice, have discussions, but in the end, take the decision that you think is right, rather than being swayed or persuaded against your better judgement. It's why you are HoD, and you will have to account for the decision and will be held responsible. It is better to be crucified (or praised) for your own decision than to take the rap for something that you didn't, in your heart of hearts, think was right in the first place.

8. '*Care but don't care*'. Caring about all members of the department is central to being HoD: it is your responsibility to look after their well-being and career as well as ensuring that they are treated fairly and have the opportunity to pursue their personal ambitions (within the constraints of the department's objectives). However, it is also important that you can switch off, and don't take this too much to heart, for two reasons. The first is your sanity; the second is so that you can remain as objective as possible. Hence this rather obscure aphorism.

9. *Say what you think, especially in meetings.* Meetings are an occupational hazard of academia. They flourish in universities, despite almost universal dislike, and as HoD you will probably find yourself in more than most. They come in a pleasing variety, from the 10 minute one-to-one, to the all day 20 person marathon. One way to amuse yourself during the latter is to calculate the cost of the meeting in time, money (in salaries and overheads), and expertise. You can then mentally ask yourself whether the outcome of the meeting will justify the use of resources, or whether they would be better employed elsewhere. Meetings can be useful for discussion before a decision, although many factors determine their success. These include knowing what the meeting is intended to achieve; ensuring pre-circulated information is relevant and

concise and not repeated during the meeting (academics tend to be good at assimilating information quickly); and ensuring that the discussion remains focused so that the meeting is kept as brief as possible. My own test of whether a meeting is worthwhile is whether anything will change for the better as a result. However, while you are in a meeting, say what you really think, rather than what you think will go down well. You are there because your views are relevant, and I have frequently heard after a meeting 'I'm glad you said that, it's what I was thinking, but didn't like to say so because ...'. If people agree with you, you have achieved something; if not, at least you have the satisfaction of knowing you have done your job. Finally, it is worth bearing in mind the adage 'The Romans didn't build an empire by having meetings'. Though it might be wise to ignore the corollary – 'they did it by killing people who disagreed with them' – however tempting it might seem at times.

10. *Minimise work that doesn't contribute to the primary goals of your department*. If you have been around universities long enough to be HoD you probably know that, if something appears crazy, it probably is. You therefore need to judge whether it is worth responding to any new memo, diktat or initiative you receive. While it is important to resist unreasonable or downright crazy requests or suggestions, it is equally important to recognise which battles you have some chance of winning, and are therefore worth fighting, rather than wasting your time and that of the staff in your department. This commandment therefore has the important sub-commandment: *have a large bin.* The 'dump, delegate, do' (in that order) principle is important: protect the staff in your department as far as possible from demands that take them away from their primary roles in research and teaching.

And finally – *DON'T PANIC.* There are bigger problems in the world, it's likely to be soluble, and the outcome is extremely unlikely to be catastrophic in the greater scheme of things. Many people shy away from the role of HoD as a thankless, paperwork-driven task, somewhere between the cleansing of the Augean stables and extracting gold from base metal, which takes you away from research. While this has elements of truth, becoming HoD also offers new perspectives and new challenges (really!), and enables you to try and help your colleagues, your department and your science in new ways. After all, academics – at least those I speak to – know to a man or woman how their department or faculty really should be run, or at least what is wrong with the way it currently is. Although there will be evenings when you want to go home and kick the cat (or at least open a bottle of wine and bore your partner with the woes of the day), being HoD can be a rewarding and frequently enjoyable job. I can think of no other job that can take you from the soldering iron in the lab, through the pleasures of research and teaching bright students, to finance, strategy and development, all coupled to a degree of relative independence and congenial colleagues. Even on a bad day, there is no other job I would rather do.

A (recovering) HoD

Coming soon: 10 fallacies of academic management; 10 things you wanted to know (or say) about university administration, 10 ways to wreck a department, 10 unexpected consequences of being HoD, 10 easy ways to annoy your HoD, the book of HoD lists, and why cats make poor academics ...

NOTICEBOARD

Institute of Zoology, Regent's Park, London, UK
4–5 December 2008
Maternal effects; evolution, physiology and implications for health and fitness
www.biology.ed.ac.uk/winterasab2008

Hilton Metropole, Brighton, UK
BPS Winter Meeting 2008
16–18 December 2008

BPS Winter Meeting 2009
15–17 December 2009
www.bps.ac.uk

Novartis Research Centre, Horsham, UK
5–6 February 2009
Ion channels as therapeutic targets
www.bps.ac.uk

AstraZeneca, Charnwood, UK
5–6 March 2009
Biochemical basis of respiratory disease
www.biochemistry.org

Justus Liebig University, Giessen, Germany
22–25 March 2009
Annual Meeting of the German Physiological Society
www.uni-giessen.de/dpg2009

Lecture Theatre, Hugh Robson Building, George Square, Edinburgh
5–7 April 2009
7th Junior Academics Meeting 2009. Molecular mechanisms in exocytosis and endocytosis. Sponsored by The Physiological Society
www.cip.ed.ac.uk/meetings

University of Leicester, Leicester, UK
20–21 April 2009
3rd Focused Meeting on Cell signalling
www.bps.ac.uk

Dresden, Germany
7–9 May 2009
New drugs in cardiovascular research
www.bps.ac.uk

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

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

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

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

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

Manly Pacific Hotel, Manly Beach, Sydney, Australia
1–4 September 2009
ISAN2009
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Motor neuron activation is conditional during muscle fatigue

The timing of the action potentials discharged by a motor neuron when it is recruited during a fatiguing contraction depends on the amount of synaptic input it requires to reach activation threshold. Action potentials are discharged continuously when the force at which the motor unit is activated is close to the target force of the contraction, but the discharge is much less regular when the target force is further below activation threshold of the motor unit


Zachary Riley (*left*) and Roger Enoka.

Most fatiguing contractions involve concurrent changes in the force capacity of the activated muscle fibres and in the level of activation of the motor unit pool (Enoka & Duchateau, 2008). Simplistically, one might expect the rate of increase in motor unit activity to match the rate of decrease in force capacity so that the muscle can sustain the force required for the task. Such a relation is not observed, however, because the properties of the motor neurons and the synaptic inputs they receive change during a fatiguing contraction. Consequently, activation of the motor unit pool must accommodate decreases in both the force capacity of the muscle fibres and the output discharged by the motor neurons.

When an individual sustains a muscle contraction at a submaximal intensity, motor units that were activated at the start of the task usually exhibit a decrease in the rate at which they discharge action potentials. To maintain the target force, the nervous system responds to decreases in discharge rate by increasing the synaptic input to the motor neuron pool. Although the increase in excitation does not prevent the decrease in discharge rate, it does activate previously quiescent motor units provided the target force is less than the upper limit of motor unit recruitment (Mottram *et al*. 2005). The discharge characteristics of the newly recruited motor units, however, indicate that the synaptic input received by the motor neuron pool during the fatiguing contraction involves more than a gradual increase in excitation.

Discharge variability

When a motor neuron is activated by the injection of a depolarizing current, the response is dictated by the intrinsic properties of the neuron and the timing of action potentials elicited by the input is more regular than that observed during activity evoked by synaptic input (Berg *et al*. 2007; Matthews, 1996). The regularity of the discharge is often expressed as the normalized variability (coefficient of variation) of the duration between consecutive action potentials, which are known as interspike intervals. When a series of brief isometric contractions are performed around the recruitment threshold of a motor unit, the interspike intervals vary across the target forces. In addition to the expected change in mean interspike interval with variation in target force, there is a change in the variability in the timing of the action potentials. The coefficient of variation for interspike interval is greatest at a target force just above the recruitment threshold of the motor unit (~30%), and then it decreases to a steady-state value (~10%) with increases in the target force (Barry *et al*. 2007; Matthews, 1996).

A motor neuron will discharge an action potential when its membrane potential is depolarized to a value that exceeds the voltage threshold for the generation of an action potential. When a motor neuron is activated during a voluntary contraction and discharges a series of action potentials, the generation of each action potential depends on the interaction between the recovery of the membrane potential from the preceding action potential and the fluctuations in membrane potential due to the continuous synaptic input received by the neuron. The influence of the synaptic input, which comprises both excitation and inhibition, on the variation in membrane potential is characterized

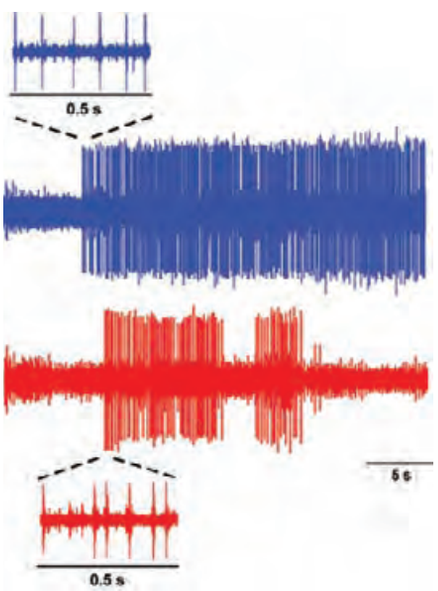

Figure 1. Representative continuous and intermittent discharge patterns exhibited by the same motor unit in biceps brachii. The blue trace indicates the discharge of the motor unit when subject held a constant force that was 4.1% below the recruitment threshold (25.1%) of the motor unit. The motor unit was recruited at 72.3 s after the contraction began and initially (see expanded trace) discharged action potentials at a rate of 13 pulses per second (pps) with a coefficient of variation for interspike interval (ISI) of 18.3%. Mean discharge rate for the period shown in the trace was 13.2 pps and the coefficient of variation for ISI was 17.5%. The red trace indicates the discharge pattern exhibited by the same motor unit when the target force was 9.5% below its recruitment threshold. The motor unit was recruited at 141.5 s after the start of the contraction with an initial discharge rate of 14.2 pps and a coefficient of variation for CV of 32.5%. Mean discharge rate for the period shown in the trace was 12.5 pps and the coefficient of variation for ISI was 29.6%.

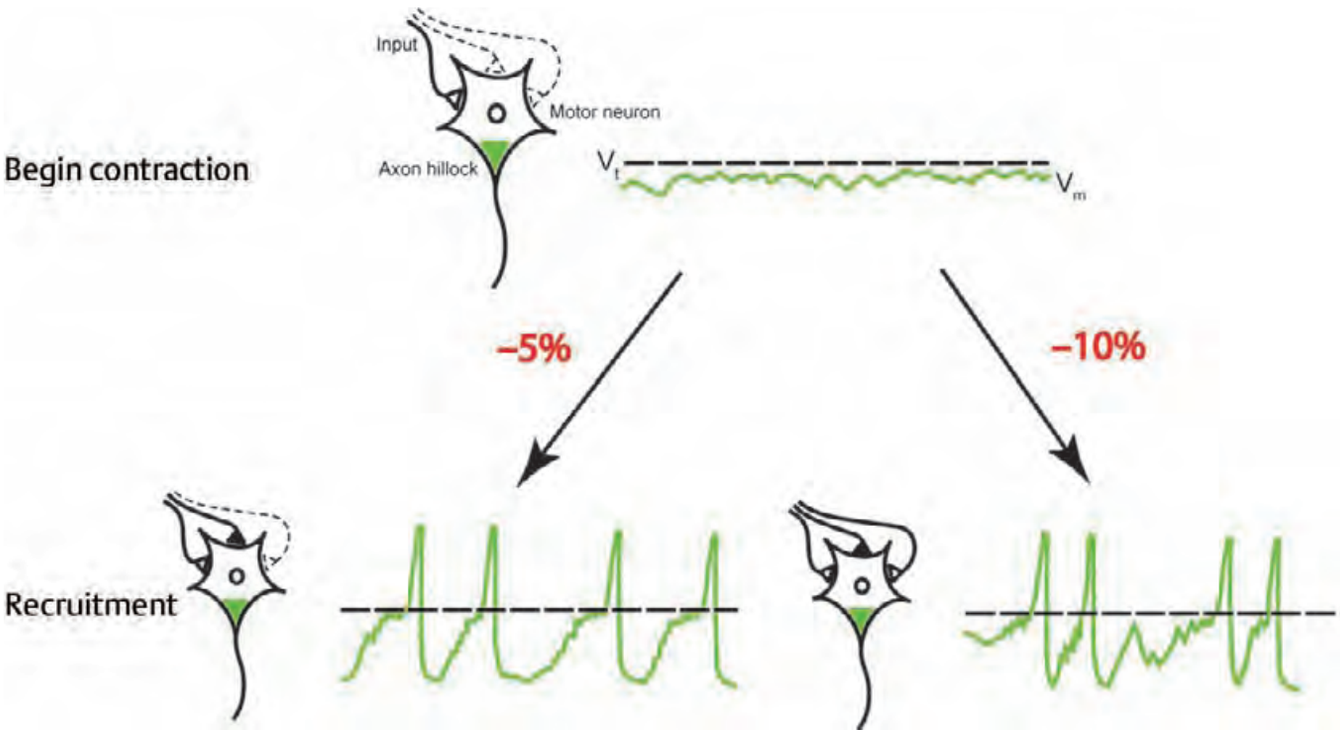

Figure 2. Scheme to explain the continuous and intermittent discharge patterns of newly recruited motor units during a fatiguing contraction. At the beginning of the fatiguing contraction (top), synaptic input causes the membrane potential (V_m) of the motor neuron to fluctuate but not to exceed its voltage threshold (V_t). As the contraction progresses, additional synaptic inputs are activated, which is indicated by the dashed lines becoming solid lines, and the membrane potential now reaches threshold and the motor neuron discharges action potentials. The synaptic inputs include both excitation (open symbols) and inhibition (filled symbols). When the target force is closer to the recruitment threshold of the motor unit (–5%), less synaptic input is required to reach threshold. When greater amounts of synaptic input are required (–10%), however, there is an increase in synaptic noise that results in more variable discharge times.

as synaptic noise. At low levels of activation, the greater variability in discharge times is attributed to action potentials being generated by transient depolarizations of membrane potential associated with synaptic noise (Matthews, 1996).

Discharge during fatiguing contractions

Motor units that are recruited at the onset of a fatiguing contraction typically experience a gradual decrease in discharge rate that is attributed to the combined effects of motor neuron adaptation and an increase in inhibitory synaptic input (Mottram *et al*. 2005). Although the progressive increase in net excitation of the motor neuron pool recruits additional motor units, the discharge characteristics suggest a significant involvement of synaptic noise in the generation of the action potentials. Riley *et al*. (2008) recorded the discharge of single motor units in biceps brachii as participants sustained an isometric contraction with the elbow flexor muscles at a target force that was less than the recruitment threshold of the motor unit. The contraction was sustained until the motor unit was recruited and discharged action potentials for several minutes. Two discharge patterns were observed: the newly recruited motor unit discharged action potentials either continuously or intermittently (Fig. 1). No motor unit exhibited both patterns during the same contraction, but individual motor units could produce both patterns in different contractions when the target force was varied.

Expression of the two patterns was related to the difference between the target force and the recruitment threshold of the motor unit. The discharge was continuous when the target force was close to recruitment threshold (~5% of maximal voluntary contraction [MVC] force), whereas it was intermittent for greater differences (~10% MVC force) between the two forces. Mean discharge rate and the variability of discharge times differed for the two patterns and from those recorded during a standardized gradual increase in muscle force when recruitment threshold was assessed.

Mean discharge rate at recruitment during the fatiguing contraction was greater and the coefficient of variation for interspike interval was lower for the continuous pattern compared with the intermittent pattern. Mean discharge rate during the sustained contraction declined during the continuous pattern but not the intermittent pattern, and the coefficient of variation remained greater for the intermittent pattern during the contraction.

Because the intermittent discharge of action potentials occurred when there was a greater difference between the target force and

recruitment threshold, the greater variability in discharge during this condition, at least at recruitment during the fatiguing contraction, might be explained by an augmentation of synaptic noise (Fig. 2). However, why the discharge variability remained elevated during the intermittent pattern and even why the discharge stopped for several seconds during the sustained contraction is more difficult to explain. Presumably, the greater net excitation required to reach threshold when the target force was further from recruitment threshold was accompanied by an increase in inhibitory synaptic input that produced a less regular discharge pattern (Berg et al. 2007).

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Levitating arms: unravelling the mystery

A Christmas party trick with an intriguing history and physiology

It's early evening after a long Christmas day and the kids are fractious. What on earth do you do next? Time for dad to produce a party trick. How about *The mysterious rising arms*? Tell your volunteer to stand in a doorway and then, with straight arms, press out as hard as possible against the door frame for a full minute. At the end of the minute the volunteer stops pushing and, after a couple of seconds, the arms rise sideways like the wings of a bird in flight (malt-fuelled grandads with dodgy hearts should not try this!). Your volunteer has just experienced the *postural aftercontraction* or, more poetically, the *Kohnstamm phenomenon* (Fig. 1). Unravelling the physiology behind this strange phenomenon has revealed fresh insights into the control of movement and posture.

The aftercontraction was first described by a neurologist, Alberto Salmon, at the 1914 meeting of the Italian Neurological Society in Florence (Salmon, 1914). The following year, an 'internist' turned psychiatrist, Oscar Felix Kohnstamm, demonstrated the same thing at the Ärztlichen Verein in Frankfurt (Kohnstamm, 1915). Kohnstamm ran a sanatorium in the Taunus Hills just outside the spa town of Königstein not far from Frankfurt. The sanatorium became fashionable amongst artists with depression, including the conductor Otto Klemperer and the expressionist painter Ernst Ludwig Kirchner. Kohnstamm's 1915 paper drew the attention of several German physiologists who began calling the aftercontraction the *Kohnstamm phenomenon*. This irritated Salmon who complained bitterly that his primacy had been poached (scientists don't change much it seems!).

The Salmon-Kohnstamm phenomenon attracted much research interest between the wars.

Martin McDonagh and Amy Parkinson.

Even Harvard professor Alexander Forbes, a collaborator of Lord Adrian, wrote a paper on what he termed 'this rather baffling phenomenon' (Forbes *et al*. 1926). Forbes experimentally rebutted the claim made by the Brazilian clinician Jayme Pereira that the aftercontraction took place without 'action currents'. Forbes noted that the electromyograph (EMG) amplitude did not remain constant once the arm moved, but grew with the movement. However, if the arm was blocked in mid movement, the EMG levelled off. Forbes took this effect as evidence of a proprioceptive influence on the motor drive.

Two years earlier, Rupprecht Matthaei at the University of Bonn found that aftercontractions were strong in axial and proximal muscles, such as the deltoid, but weak or absent in the hand and other distal

Figure 1. Neurologist Alberto Salmon with a patient in 1916. The patient is experiencing an after contraction following a voluntary abduction of the arms against fixed resistance provided by the clinician.

muscles (Matthaei,1924). I (MM) took Matthaei's observations as a clue that postural control systems might be involved, including the vestibular apparatus. To investigate a possible vestibular influence on aftercontractions in the deltoid muscle we strapped our subjects on their backs to a rotating board, which could be fixed at any inclination. At each inclination we suspended the subject's arms from slings. These tricky but enjoyable (at least for the experimenter) experiments revealed a linear relationship between the body inclination and the amplitude of the aftercontraction EMG. This clear result was pleasing but not decisive, as the gravitational load on the arms also varies with body inclination. Could load be a more important signal than vestibular input in driving the phenomenon? We decided to go back to where Forbes had left off and to ask the questions : What is the proprioceptive influence? How does it work? And which receptors are involved?

In the next experiments we varied the load on the arm whilst holding the vestibular signal constant. The subject sat on a chair with the head supported and to simplify the procedures we used only one arm. The gravitational load on the muscle increases as the limb moves towards the horizontal, so we used a counter lever to nullify this effect (Fig. 2) (Parkinson & McDonagh, 2006). In later experiments we added the experimental loads via a pulley wheel so that muscle loading remained the same at each joint angle. (Parkinson & McDonagh, unpublished). The results of these experiments are illustrated in Fig. 3. We found that the strength of the aftercontraction depends on both load and joint angle. Earlier experiments revealed that the size of the response increased with muscle shortening and decreased with muscle lengthening(Adamson & McDonagh, 2004) .This is very reminiscent of Sherrington's shortening and lengthening reactions and also to the release of muscle cramps by stretching. Perhaps they share a common mechanism?

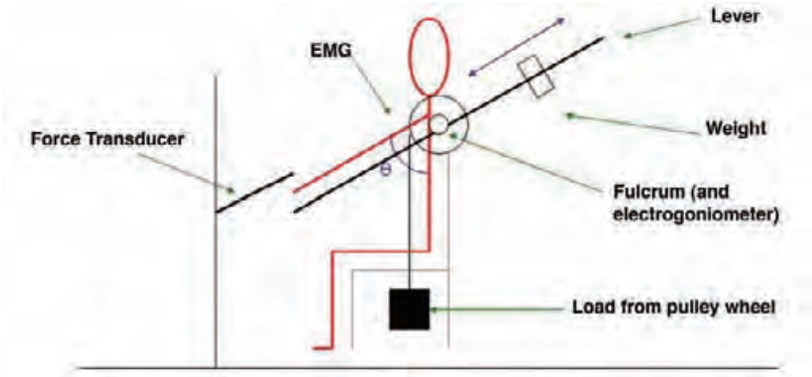

Figure 2. Recording the aftercontraction. The weight of the arm is balanced by a counter lever with an adjustable weight. This removes the variation of gravitational load with arm position. A range of experimental loads are added via a pulley wheel so that the loading is constant throughout the movement range. EMG signals are recorded from the Deltoid muscle and shoulder rotation angle is recorded by an electrogoniometer.

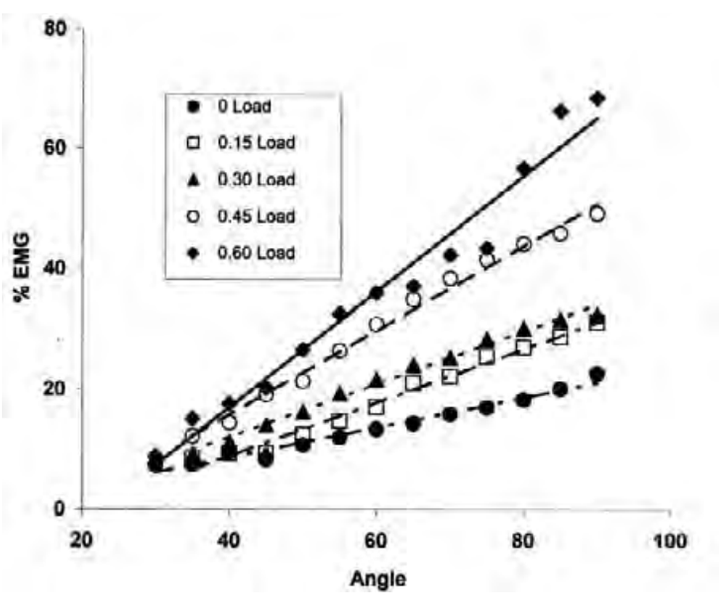

Figure 3. After contraction EMG amplitude through the range of movement at a range of loadings. Loading are fractions of the total load of a free arm unbalanced by a counter lever. At 0 load the arm is exactly balanced by the counter lever at all angles. EMG amplitude is expressed as a percentage of the EMG during the standard voluntary precontraction. Angle in degrees between arm and trunk. Data from 10 subjects.

Next, we asked: Does joint angle directly modulate the EMG, or is the source some other factor which is varying with angle, such as muscle spindle length? In our more recent experiments we have tried to separate these two variables. The subject performs the 60s pre-contraction (see beginning of article) at a variety of joint angles. Activation of gamma, as well as alpha, motorneurones during the 60s precontraction will cause the sensory region of the muscle spindle to be tightened by gamma action. This tightening should result in a similar spindle output at a range of initial joint angles. If the spindle signal modulates the aftercontraction EMG, then the EMG will have a closer relationship to the presumed spindle length than to the absolute joint angle. This is exactly what we found (Fig. 4; McDonagh & Parkinson, unpublished); the tight relationship of emg amplitude to joint angle seen in Fig. 3 broke down. A future step is to test the spindle hypothesis by direct microelectrode recording from the spindle afferents in sensory nerves during aftercontractions.

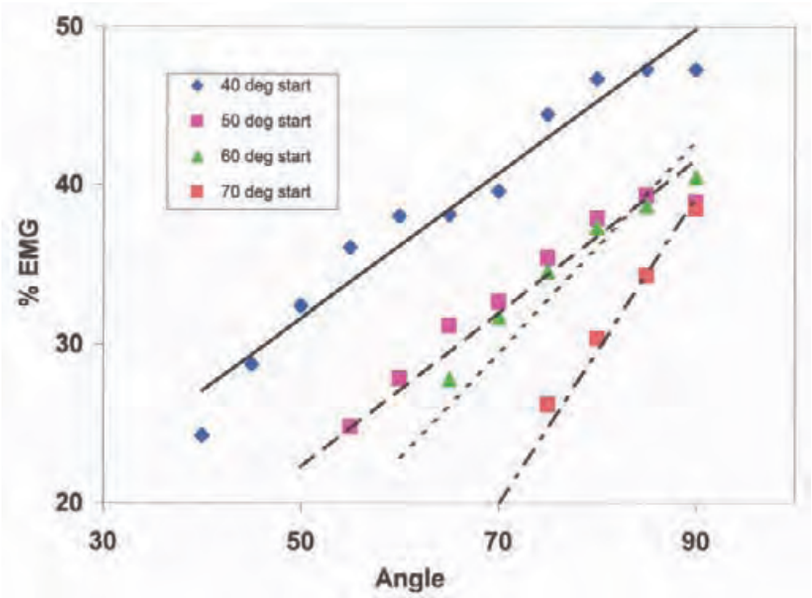

Figure 4 . Effect of different starting angles on aftercontraction EMG. The isometric precontraction was performed at 40, 50, 60 and 70 deg and the aftercontraction ensued. The EMG was then sampled over the angular range. Loading was 0.25 (see legend fig 2) under all conditions. EMGg amplitude is expressed as a percentage of the EMG during the standard voluntary precontraction. Angle in degrees between arm and trunk. Data from 13 subjects.

To summarise so far: the aftercontraction is driven by the nervous system. It is not an intra-muscular contracture. Loading and muscle shortening strengthen it and forced lengthening weakens it. The proposed sensory receptors are Golgi tendon organ load receptors and muscle spindle length receptors.However, to fit with the data this would require positive force feedback from the tendon organs and negative length feedback from the spindles, the exact opposite of what is produced by the known spinal circuits. This suggests control from supraspinal centres capable of more complex processing. Which areas of the CNS could be generating the motor drive?

Over the years, the brain stem, basal ganglia, cerebellum and motor cortex have all had their advocates, who have based their guesses on argument and weak circumstantial evidence. Some have regarded it as a purely spinal phenomenon with no involvement of higher centres. Recently we took a direct approach by taking fMR images of the brain during aftercontractions. We found (Parkinson & McDonagh, unpublished) that the motor cortices are indeed involved in the phenomenon, as is the anterior cingulate cortex (ACC), an area of brain which has been implicated in error processing. In voluntary movement, predicted sensory outcome and actual sensory outcome match. In the after-contraction movement there is no motor command and so no predicted sensory outcome to match the actual one. Perhaps the ACC is processing this error signal.

It is now clear that the aftercontraction has both proprioceptive and central components – so how does the complete response come about? Our current hypothesis is as follows. During the 60s voluntary isometric pre-contraction, the system controlling the arm adapts to a strong opposing force. It changes its stored value of motor drive for this position. Once the pre-contraction ceases, this adaptation is still present. When this drive is released, as the aftercontraction, it produces more force than needed to maintain arm position against gravity, so the arm moves. Once the arm starts to move the motor drive is increased by two positive proprioceptive influences, muscle shortening and muscle load.

Most of our motor acts are carried out unconsciously. The after-contraction fMRI vividly illustrates that even the most simple of motor acts involves large areas of the cerebral cortex. Furthermore, the proprioceptive mechanisms involved in aftercontractions almost certainly underlie the everyday control of limb orientation in a gravitational field. These positive force feedback, and negative length feedback, mechanisms are fruitful areas for future research in movement neuroscience. In conclusion, the aftercontraction is an intriguing phenomenon in itself, but its study can also make a valuable contribution to our general understanding of motor control. Not bad for a party trick.

Visit http://www.metacafe.com/watch/323026/make_your_arms_levitate/ to watch a video of arm levitation.

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A little bit of ammonium may be good for your brain

Although specific ammonium-transporting proteins are well known in bacteria and plants, only recently has molecular and functional evidence begun to accumulate for ammonium transporters in animals. We describe how an ammonium transporter on the glial cells of bee retina plays an essential role in energy metabolism, and suggest an update of an old idea of a neuron-astrocyte flux of ammonium at synapses in mammalian brain

Ammonium transporters are widespread

It is convenient to use the word 'ammonium' to include NH_4^+ (the 'ammonium' of chemists), NH_3 ('ammonia') and the mixture of the two that spontaneously forms in water. At physiological pHs the equilibrium mixture contains about 98% NH_4^+ and 2% NH_3 (see Marcaggi & Coles, 2001). NH_3 can diffuse through lipid membranes (although not nearly as well as oxygen does). As shown by measuring intracellular pH, if you add NH_4Cl outside a cell, NH_3 entering the cell tends to alkalinize the cytoplasm because about 98% of the NH_3 combines with H^+ (Fig. 1). In practice, some ammonium goes in as NH_4^+, not NH_3. A small fraction (about 2%) of this entering NH_4^+ dissociates to form NH_3 and some H^+ ions: the entering flux of NH_4^+ would have to be more than about 50 times that of NH_3 to produce a *net* acid shift. In most cells there is an initial alkalinisation caused by NH_3 entry, then NH_4^+ entry produces a slow secondary acidification, but in some cells there is a primary acid shift, indicating that they take up overwhelmingly the NH_4^+ form[1]. The NH_4^+ ion is about the same size as a K^+ ion and the conservative suggestion was that NH_4^+ was just leaking in via K^+ channels or transporters. However, proteins of the Rh family (notorious for the immune reactions of Rh(-) foetuses to the blood of a Rh(+) mother) which are expressed not only in erythrocytes but also in kidney, liver, testes and parts of the brain, have homology with the Amt family of ammonium transporters,

[1] It is easy to get the textbook alkaline response: you simply use a damaged cell with an unphysiologically low intracellular pH.

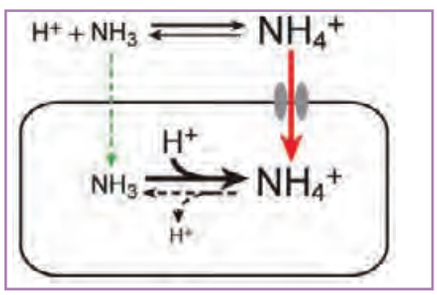

Figure 1 (*left*). Ammonium entry into a cell. Entry of NH_3 produces a large alkalinisation. Entry of a similar amount of NH_4^+ produces a much smaller acidification.

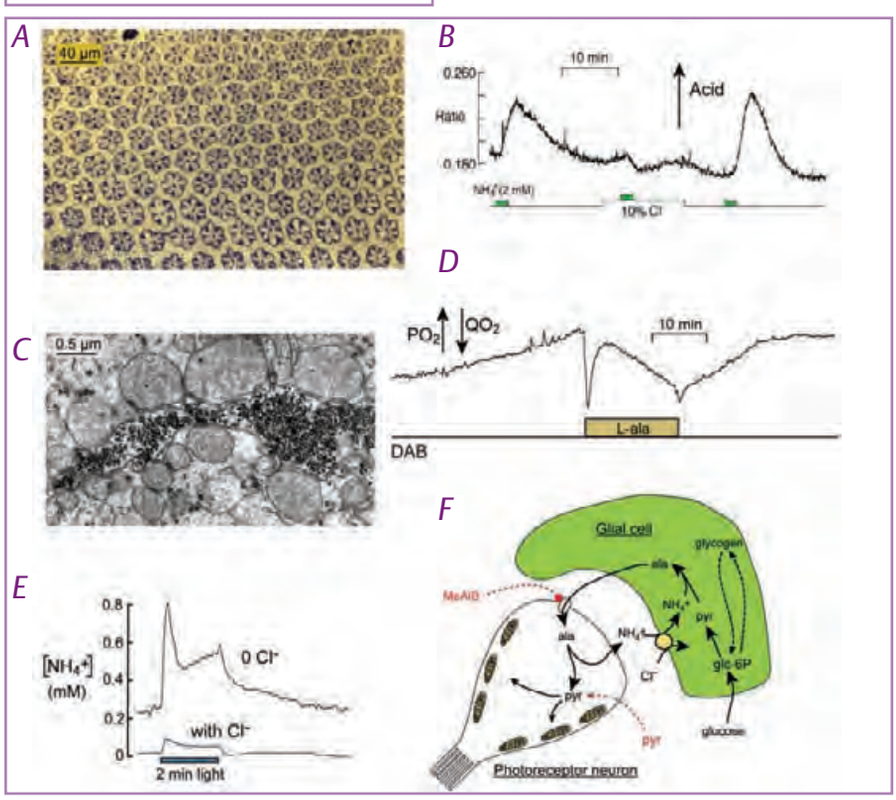

Figure 2. *A*, A section through a drone retina. Each rosette is composed of six, large, identical photoreceptors, 450 µm long, which receive light passing through one corneal facette. Each rosette is surrounded by about 35 glial cells. There are no blood vessels or chemical synapses (micrograph by PM Orkand). *B*, Application of ammonium (green rectangles) acidifies an isolated bundle of glial cells, and this acidification is blocked when the concentration of Cl^- is reduced. This suggests NH_4^+-Cl^- cotransport (from Marcaggi *et al* [1999]. *Eur J Neurosci* **11**, 167–177). *C*, An electron micrograph showing part of two glial cells, packed with glycogen granules, and part of a photoreceptor containing many mitochondria (from A Perrelet). *D*, PO_2 in a bee retinal slice measured with an O_2 microelectrode. DAB, present throughout this recording, reduces supply of fuel from glial glycogen so consumption of O_2 (QO_2) falls and PO_2 rises. Application of alanine restores consumption. *E*, $[NH_4^+]$ in extracellular clefts. In normal Ringer solution, $[NH_4^+]$ was hardly detected in the dark or during light stimulation of the photoreceptors ("with Cl^-"). When glial uptake was reduced by removing Cl^- ("0 Cl^-") a much greater $[NH_4^+]$ signal was measured. *F*, Scheme of metabolic exchange in drone retina. Methylaminoisobutyrate is thought to reduce alanine uptake (red dot), and pyruvate bypasses the alanine flux (red arrow). (Figs. *D*, *E*, *F* adapted from Coles *et al*. 2008) .

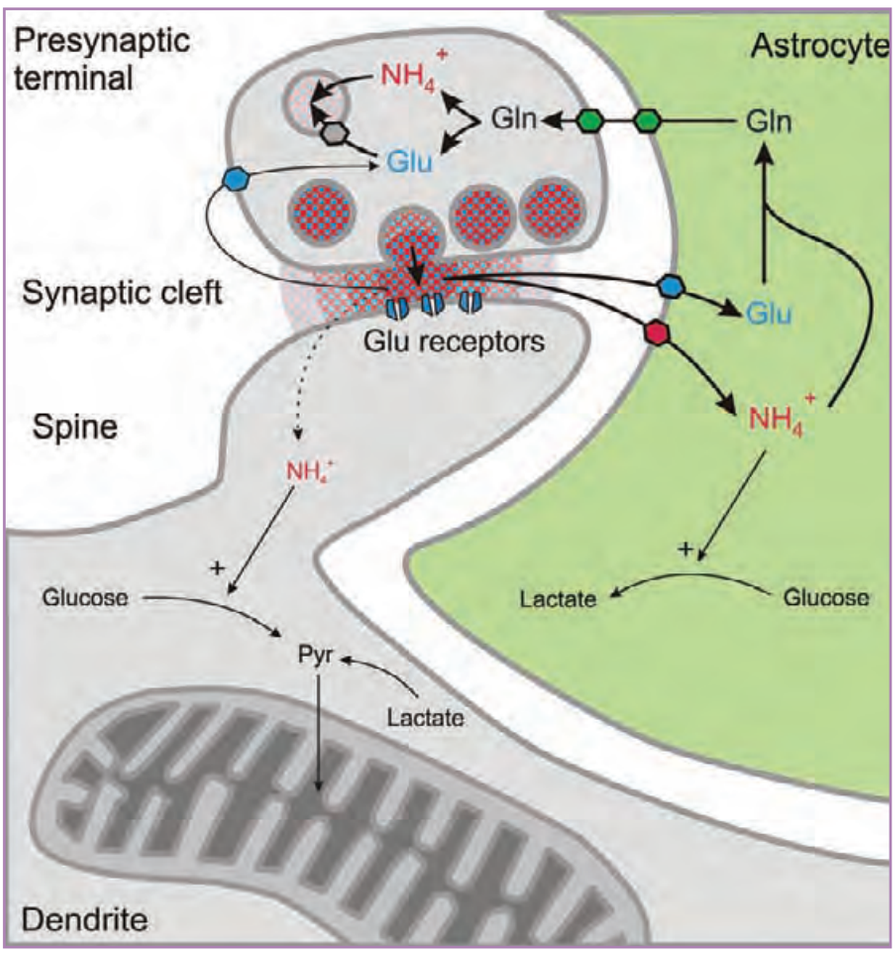

Figure 3. The glutamate/glutamine shuttle at a vertebrate glutamatergic synapse showing the ammonium flux suggested by Benjamin & Quastel (1975), and the accumulation of ammonium together with glutamate in the synaptic vesicles suggested by Marcaggi (2006).

found in apparently all organisms up to and including invertebrates (Huang & Peng, 2005).

There is general agreement that Amt and Rh proteins have an external binding site for NH_4^+, but lively debate about what happens next. One possibility is that a proton is stripped off NH_4^+ to leave NH_3 which passes through a channel, but there are also reports of electrogenic transport, i.e. transport of NH_4^+ or cotransport of NH_3 and H^+ (Javelle *et al.* 2008). Surprisingly, although Amt/Rh proteins are so widespread, the first ammonium transport selective for NH_4^+ over K^+ to be demonstrated in an animal cell appears to be by another, molecularly different variety of ammonium transporter found in the honeybee retina.

[2] 1,4-Dideoxy-1,4-imino-D-arabinitol.

A NH_4^+-selective cation-Cl^- co-transporter on glial cells of the bee retina

The drone (male) honeybee has a large eye, which is useful for spotting high-flying queens, and whose retina is composed almost exclusively of photoreceptor neurons and a homogeneous population of glial cells, arranged with impressive regularity (Fig. 2*A*). When the intracellular pH of retinal glial cells is measured with a pH-sensitive fluorescent dye, application of ammonium is found to produce a robust intracellular acidification that is abolished in the absence of Cl^- (Fig. 2*B*). This suggests co-transport with Cl^-. The transporter is selective for NH_4^+ over K^+ (Marcaggi & Coles, 2000), but it shares with a wide range of K^+-Cl^- cotransporters the presence of inhibitory binding sites for bumetanide and piretanide.

These results suggest a NH_4^+-Cl^- cotransporter which may be molecularly related to K^+-Cl^- cotransporters, but which is different from ammonium transporters of the Amt/Rh superfamily. The bee genome includes three Amt/Rh genes, thus making a minimum possible total of four ammonium transporters in this species.

NH_4^+-Cl^- cotransport is central to energy metabolism in bee retina

A long series of papers have shown that, in drone retina, glucose is taken up exclusively by the glial cells, where it is converted to pyruvate then alanine. Tsacopoulos *et al*. (1994) proposed that the alanine is transferred to the photoreceptor neurons where it is deaminated to provide pyruvate for the numerous mitochondria (Fig. 2*C*), and that ammonium is returned to the glia, to support sustained production of alanine from glucose or glycogen. Two experimental tools not available to the earlier workers have recently been used to test and refine this model (Coles *et al.* 2008). First, it was not known whether these neurons can actually use alanine as a fuel. Normally, in a retinal slice, the huge stocks of glycogen in the glia provide a supply of fuel to the neurons that lasts for many hours. This supply can be reduced by DAB[2], an inhibitor of glycogen phosphorylase, as can be seen by a fall in O_2 consumption by the mitochondria (present only in the neurons). It was found that application of alanine restored O_2 consumption, as predicted (Fig. 2*D*). Second question: do the photoreceptors release ammonium? Instead of trying to guess ammonium movements from measurements of pH, the authors used a triple-barrelled ammonium-sensitive microelectrode to directly measure $[NH_4^+]$ in the extracellular clefts. In normal Ringer solution, extracellular $[NH_4^+]$ was below the detection limit of these electrodes. However, when NH_4^+ uptake by the glia was blocked by removing Cl^- from the Ringer solution,

extracellular [NH_4^+] was measurable in the dark and shown to increase during light stimulation (Fig. 2*E*). Extracellular [NH_4^+] was greatly reduced by methylaminoisobutyrate, a blocker of amino acid transport, and also by pyruvate, which was expected to provide a direct substrate for the mitochondria, bypassing alanine (Fig. 2*F*). Hence, in this preparation, we now have very strong evidence for the neurons being fuelled by alanine, with ammonium being returned to the glial cells and taken up by a specific transporter.

A neuron-astrocyte ammonium-amino acid shuttle in mammalian brain?

Mammalian astrocytes (at least in culture) avidly take up NH_4^+ (see Marcaggi & Coles, 2001). Most of the glutamate released at glutamatergic synapses in the mammalian brain is taken up into astrocytes by glutamate transporters where, in the astrocytes, it reacts with ammonium to form glutamine. Glutamine, which does not bind to synaptic receptors, is transferred back to the pre-synaptic terminals and deaminated to glutamate. By analogy with bee retina, the shuttle might be completed by transfer of ammonium from the neurons to the astrocytes, as originally proposed by Benjamin & Quastel (1975). Fig. 3, is an update of this proposal which shows uptake of NH_4^+ rather than NH_3, and the co-release of ammonium with neurotransmitters (Marcaggi, 2006).

Within the astrocyte, ammonium might act as a signal as well as a reactant. For example, enzymes of the glycolytic pathway are stimulated by ammonium and exogenous ammonium does increase lactate production in rat brain *in vivo* (Provent *et al.* 2007). What would really help this field is a good membrane permeable ammonium-sensitive fluorescent indicator. Please tell your chemist friends.

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The Editor-in-Chief works closely with the Managing Editor, Carol Huxley, and her staff at The Society's Publications Office based in Cambridge, UK. The Editor-in-Chief chairs regular meetings of *The Journal*'s Executive Committee, comprising Senior Editors and representatives of The Society and the publishers (Wiley-Blackwell). This Committee is responsible for strategic planning and operational matters relating to *The Journal*. Serving under the Senior Editors is an international Editorial Board of over 50 members, which meets annually.

Candidates should submit a CV together with a letter of no more than three pages of A4 by 1 December 2008 summarising the following:

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Going to the US next year?

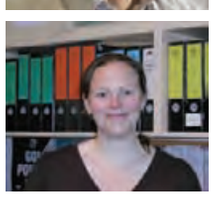
If you are travelling to the USA after 12 January 2009 under the Visa Waiver Program you will need to apply for advance authorization using the online process available at https://esta.cbp.dhs.gov.

How many sensors in the bladder?

Sensory neurons projecting from the urinary bladder (bladder afferents) play a key role in neural circuits underlying both urine storage and normal micturition. They are responsible for all sensations from the bladder such as fullness, the urge to micturate, discomfort and pain. Afferents from different regions of the bladder probably have characteristic receptive fields, response properties and conduction velocities. Indeed, recent experiments *in vitro* have identified several distinct functional classes of bladder afferents. How then can we relate the functions of various types of afferents in normal and pathological states of the urinary bladder?

Based on their conduction velocities, bladder afferents comprise two main groups: faster conducting, thinly myelinated Aδ-fibres; slower conducting unmyelinated C-fibres. In cat bladder, most Aδ-fibres are distension-sensitive, while C fibres are not (Janig, 2006). In rats, however, about 50% of C-fibres respond with low threshold to bladder distension (Shea *et al*. 2000). Overall, most bladder afferents seem to be polymodal, since they can respond to both mechanical and chemical stimuli (Daly *et al*. 2007; Rong *et al*. 2002; Xu & Gebhart, 2008; Zagorodnyuk *et al*. 2007). Nevertheless, there is considerable diversity in the range of stimuli that activate different classes of bladder afferents.




Clockwise from top left: Vladimir Zagorodnyuk, Ian Gibbins, Marcello Costa, Sarah Gregory and Simon Brookes.

Mechanoreceptors

Most studies of bladder afferents *in vivo* have identified mechano-receptors that fire in proportion to intravesical pressure, reflecting the combination of passive distension and active contraction of the bladder wall. Thus, they behave as bladder wall tension receptors. Experiments *in vitro* have revealed three distinct classes of stretch-sensitive afferents that behave as tension receptors: low threshold mechanoreceptors in the muscle layer; mechanoreceptors at the interface between muscle and mucosa (muscle-mucosal mechanoreceptors); and high threshold mechanoreceptors in the muscle layer (Daly *et al*. 2007; Rong *et al*. 2002; Xu & Gebhart, 2008; Zagorodnyuk *et al*. 2007). There also may be 'volume' receptors, which sense bladder distension irrespective of pressure (Morrison, 1999).

It is widely believed that low threshold mechanoreceptors are involved in non-painful sensation from the bladder and contribute to reflex regulation of bladder contractility. In contrast, high threshold afferents mediate discomfort and painful sensations from the bladder (de Groat, 2006; Janig 2006). However, this division has numerous pitfalls. Firstly, low threshold, wide dynamic range mechanoreceptors encode a large range of mechanical stimuli (distension and contraction) extending into the noxious range. Secondly, only some high threshold mechanoreceptors respond to distension (Janig, 2006). To complicate matters further, some low threshold mechanoreceptors express capsaicin-sensitive TRPV1 receptors (Daly *et al*. 2007) that normally are associated with functional nociceptors.

Chemoreceptors

It is still unclear whether pure chemoreceptors exist in the bladder or if chemoreception is mediated by polymodal stretch-insensitive mechanoreceptors. Some bladder afferents are excited *in vivo* only by distension with isotonic KCl, but not NaCl, and these afferents have been considered to be chemoreceptors (Moss *et al*. 1977). Stretch-insensitive afferents activated by chemical stimuli (capsaicin, hypertonic solution, α,β-methylene ATP) *in vitro* probably correspond to chemoreceptors described *in vivo*. However, the same fibres also respond vigorously to gentle mucosal stroking (mucosal high-responding mechanoreceptors), indicating that they are actually polymodal afferents (Zagorodnyuk *et al*. 2007). Patients with interstitial cystitis have enhanced sensitivity to intravesicular instillation of hypertonic KCl solutions, suggesting that some of their symptoms may be due to increased firing of afferents with these properties.

Nociceptors

A widely-used classification identifies two broad categories of small diameter, slowly-conducting nociceptive neurons:

- those expressing neuropeptides [typically, substance P (SP) and calcitonin gene-related peptide (CGRP)] plus TRPV1 and TrkA receptors;
- those that do not, but which are labelled by the isolectin B4 (IB4), and depend on glial-derived neuronotrophic factor (GDNF) for postnatal survival.

However, this is almost certainly a misleading simplification.

Potentially nociceptive C-fibre neurons comprise a functionally diverse array characterised by differential expression of various TRP

and ASIC channels responding to temperature and pH, TTX-resistant Na^+ channels (Nav1.8 and 1.9) and a range of K^+ channels (Fang *et al*. 2006). How these functional characterisations correlate with the broad neurochemical categories is still largely unresolved. For example, intravesical instillation of capsaicin, which opens TRPV1 channels, produces burning pain in humans or pain-related behaviour in animals. However, in guinea pig bladder, capsaicin activates at least two different classes of mechanoceptive afferents: high threshold stretch-insensitive mechanoreceptors and the mucosal high-responding mechanoreceptors which are presumably activated in damaged or inflamed urothelium (Zagorodnyuk *et al*. 2007).

As with other nociceptors, both low and high threshold mechanoreceptors in the bladder show sensitisation by inflammatory mediators, such as cytokines, α,β-methylene ATP or as a result of cystitis (Rong *et al*. 2002; Roppolo *et al*. 2005; Xu & Gebhart, 2008). Thus, noxious stimuli in the urinary bladder probably are detected by thin myelinated Aδ- and unmyelinated C-fibres alike, both of which include low and high threshold mechanoreceptors.

'Silent' afferents

Up to about 30% of afferent to the bladder apparently do not respond to any level of distension and have been called 'silent afferents'. However, acute inflammation induces some previously 'silent afferents' to become spontaneously active and develop a degree of mechanosensitivity. Thus, they may contribute to nociception from the inflamed bladder (Janig, 2006). A subset of them may represent stretch-insensitive mechanoreceptors with endings in the mucosa (mucosal low responding mechanoreceptors). So-called 'cold receptors' that express TRPM8 (a TRP channel responsible for detecting cold stimuli) probably represent another class of 'silent nociceptors' in the bladder, since their density is increased in the suburothelium of overactive and painful bladders (Mukerji *et al*. 2006).

Linking structure and function

It is commonly believed that all visceral afferents have unspecialised bare endings (Janig, 2006). In rats, only 50–60% of spinal sensory neurones projecting to the bladder are labelled with neuropeptides such as CGRP. So far we do not have a reliable neurochemical marker for visceral afferent endings that do not express neuropeptides. Consequently, nearly half the bladder afferents never have been specifically visualised. Now, however, we can reveal non-peptide bladder afferents by anterogradely labelling functionally-characterised fibres with biotinamide (Fig. 1). Following this procedure, several morphological types of bladder afferent endings can be seen: 'antenna-like endings' in the muscle layers, 'grape-like-endings' in the lamina propria; and free varicose endings in the lamina propria (Fig. 1*C*, *D* & *F*). Most probably, 'antenna-like endings' correspond to muscle mechanoreceptors, while 'grape-like endings' are muscle-mucosal mechanoreceptors. Free nerve endings containing CGRP and SP in the lamina propria (Fig. 1*E* & *F*) probably represent capsaicin-sensitive mucosal mechanoreceptors, since removal of the urothelium both abolished their response to light von Frey hair stroking (Zagorodnyuk *et al*. 2007) and produced significant damage of

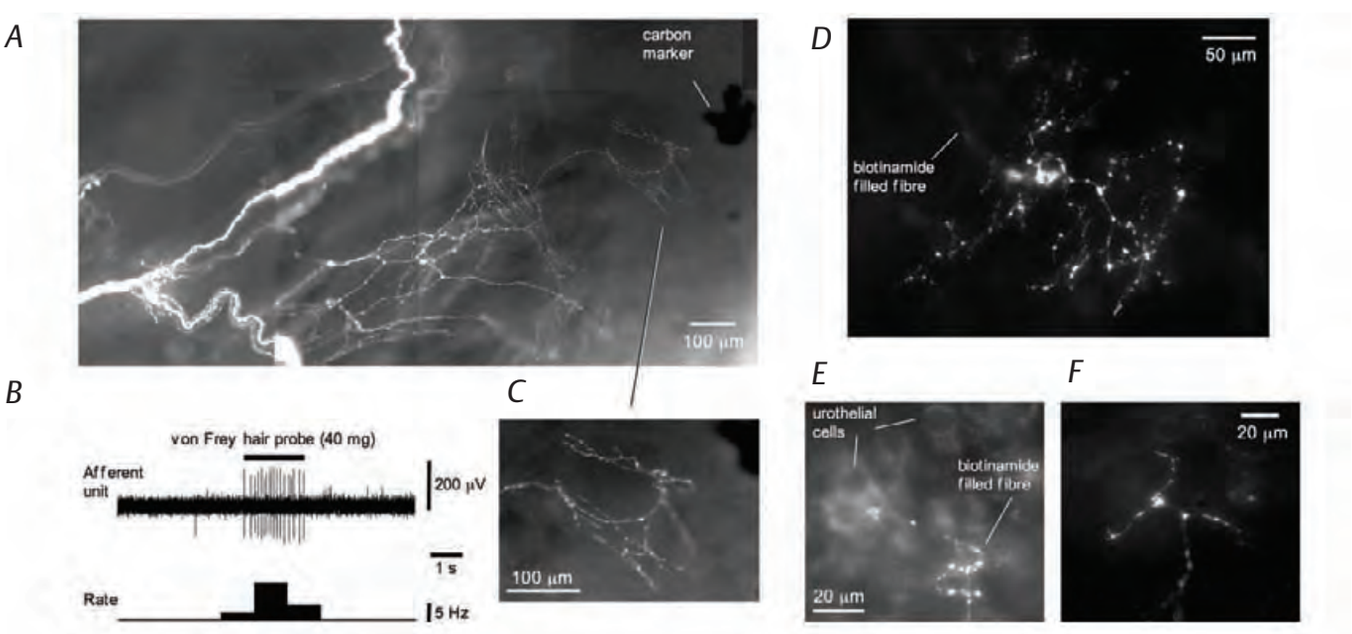


Figure 1. Visualising functionally defined bladder afferents. *A*, Biotinamide-filled nerve trunk including a stretch-sensitive muscle mechanoreceptor. *B*, probing of receptive field of this afferent with a von Frey hair evoked firing only in a discrete spot (hotspot, marked by carbon particle). *C*, 'antenna-like ending' associated with the hotspot. *D*, single biotinamide-filled fiber gave rise to 'grape-like endings' in the lamina propria. *E*, biotinamide-filled fiber near urothelial cells. *F*, CGRP-immunoreactive free ending in the lamina propria near the urothelium.

SP- and CGRP-positive nerve endings in the lamina propria.

Clearly, there is great complexity in the sensory innervation of the bladder. There must be around 10 distinct functional classes, each of which has a precise role in signalling the mechanical and chemical environment of the bladder. An immediate challenge is to characterise each of them fully according to morphological, functional, pharmacological and immunohistochemical criteria. Only then, will we be able to determine which populations of afferents are most important clinically, and most amenable for pharmacological manipulation in the treatment of bladder disorders.

Acknowledgements
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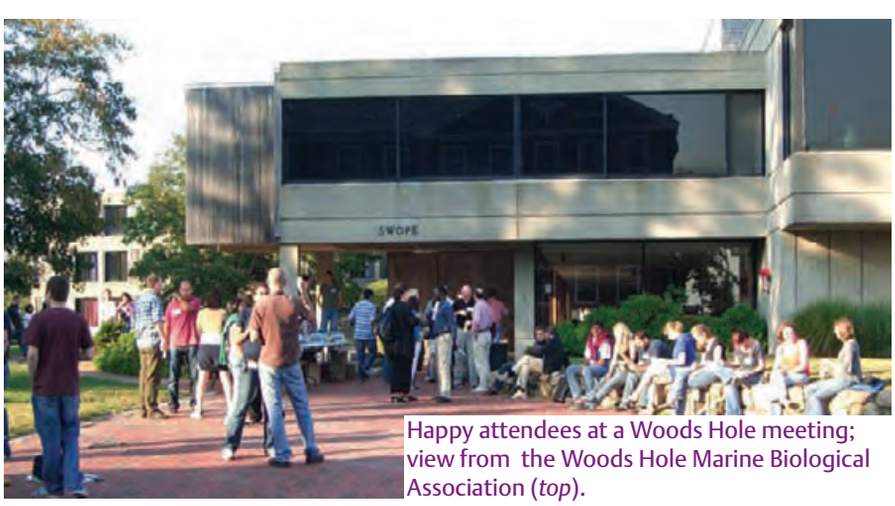

Happy attendees at a Woods Hole meeting; view from the Woods Hole Marine Biological Association (*top*).

Make waves for Woods Hole

Start planning for The Society's 2009 joint meeting with the Society of General Physiologists

Have you ever been to Wood's Hole? On the beautiful New England seaside, this is the setting for the joint Society of General Physiologists and The Physiological Society meeting to be held from 9–13 September 2009.

The organizers (David Eisner and Lee Sweeney) are putting together a first rate and diverse programme on the overall theme of *Muscle in health and disease*, running the gamut from molecular studies of motor function to diseases of skeletal, cardiac, and smooth muscles.

In this meeting, The Physiological Society is an equal participant with the Society of General Physiologists and so, for the first time ever in North America, The Society will have a real presence, and the meeting should be small enough and friendly enough for all. This will be a chance to go to a beautiful, unspoiled place in America at the best time of year. In September the temperatures are usually in the 70–80°s (22–27°C), and the sea is warm enough to swim in. A ferry boat ride to Martha's Vineyard or a dedicated whale- watching trip make for a non-standard Society experience and, aside from nightly mixers around the posters, and a traditional New England lobster feast, there are several classic inns, restaurants and bars around Woods Hole and nearby Falmouth. Take a look at the SGP website (http://www.sgpweb.org/), then start making plans to join what promises to be a fantastic meeting.

Colin Nichols

Does muscle pain increase muscle stiffness?

Animal studies have shown that muscle pain can reflexly excite gamma motor neurones and thus increase muscle spindle stretch sensitivity and discharge rate. According to the popular, but clinically unproven, hypothesis this reflex loop may perpetuate into a sustained 'vicious cycle' - reciprocally aggravating muscle tone and pain. Yet a lack of clear experimental evidence – and recently obtained new data in humans that contradicts this notion – has cast doubt on whether this model can be used to explain physiological mechanisms and translate into the development of treatments

Chronic musculoskeletal pain syndromes (CMPS) are a common group of, usually, activity and work-related myalgias. Unfortunately, the efficiency of treatments available today is very limited, partly because the physiological mechanisms underlying the clinical conditions are not well understood. One of the hypotheses – developed by Peter Sojka and the late Håkan Johansson in Umeå, Sweden – suggests that chronic muscle pain may develop as a result of a 'vicious cycle' reflex initiated by nociceptive input itself (Johansson & Sojka, 1991). This hypothesis is based on an elegant set of experiments in the anaesthetised animals demonstrating that nociceptive afferents excite γ-motor neurones and thereby increase stretch sensitivity and discharge rate of the muscle spindles. The resultant excitation of the homonymous α-motoneurone pool may lead to increased muscle tone, contraction-induced ischemia and accumulation of metabolites (Johansson & Sojka, 1991). If the production of metabolites is reasonably high to excite nociceptors, a process sustaining a 'vicious cycle' might be initiated, resulting in a chronic muscle pain.

Alexander Burton (*left*), Ingvars Birznieks and Vaughan Macefield.

In contrast to animal experiments, to date clear experimental evidence in humans is lacking. Variable results have been obtained when attempting to demonstrate these effects in human subjects by looking at EMG activity, stretch reflexes and proprioceptive function; nevertheless, they all agree that the 'vicious cycle' mechanism is very unlikely.

Due to methodological limitations the conclusions in regard to modulation of muscle spindle activity in humans so far have been based on indirect experimental evidence. However, our recent study

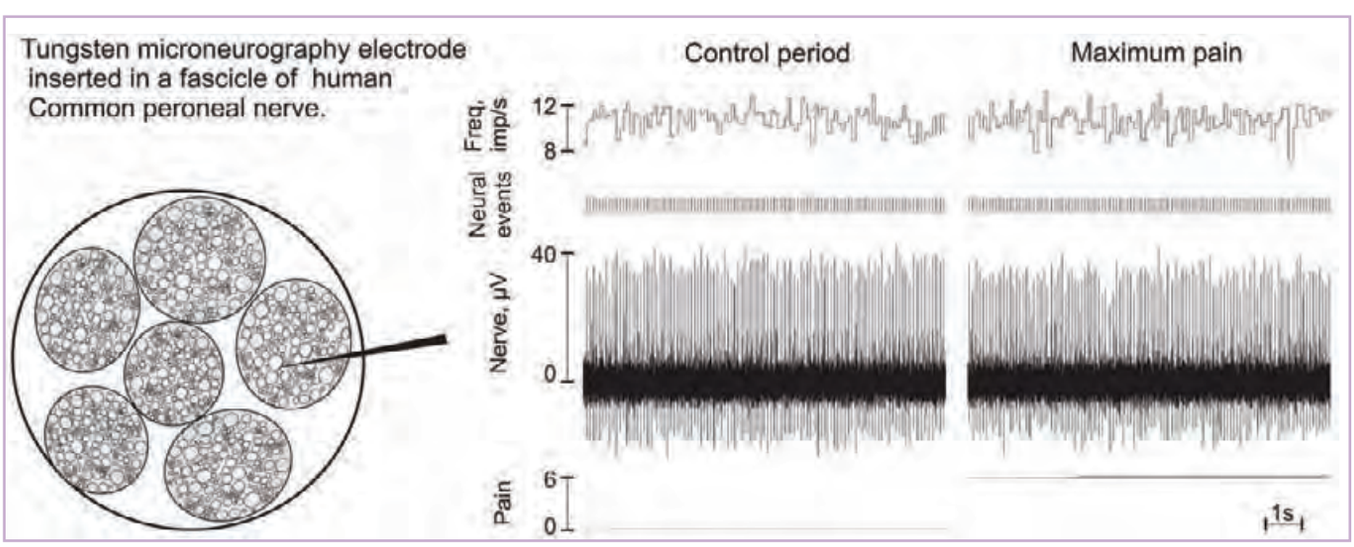

Figure 1. Microneurographic recordings from the common peroneal nerve in an awake human subject. Examples of discharge activity of single muscle spindle afferent recorded before and during experimentally-induced muscle pain. This sensory unit was classified as a Ia muscle spindle afferent innervating a peroneus muscle. Despite the strong pain (rated 6 on a 0–10 scale) the instantaneous discharge rate was not affected by nociceptive stimulation. Leg muscles remained relaxed throughout the experiment and there was no surface EMG activity detected. Experimental muscle pain was induced by bolus intramuscular injection of 0.5ml 5% hypertonic saline into tibialis anterior (modified from Birznieks *et al.* 2008).

has overcome those constraints by using microneurography to record discharge activity of single human muscle spindle afferents during experimentally-induced pain in muscle and skin (Fig. 1) (Birznieks *et al.* 2008).

Unitary recordings were made from 14 primary and six secondary muscle spindle afferents, located in the ankle or toe extensors or the peronei muscles, via microelectrodes inserted into the common peroneal nerve. During muscle pain, induced by intramuscular injection of 0.5 ml of 5% hypertonic saline, no afferents increased their discharge activity in response to static stretch, moreover the overall net discharge rate decreased during muscle pain by 6.1%. During skin pain, induced by a subcutaneous injection (0.2 ml), only small changes in afferent activity were observed and the overall net discharge rate remained essentially the same.

To support the 'vicious cycle' hypothesis, nociceptive excitation of fusimotor drive must be substantial. Experiments on anaesthetised cats, conducted in a comparable experimental setup to our study, demonstrated a substantial reflexogenic increase in mean discharge rate by ~80% in afferents innervating homonymous as well heteronymous muscles (Thunberg *et al.* 2002). This was not the case in our human microneurography experiments, firmly contradicting animal data and thus questioning the clinical relevance of the 'vicious cycle' hypothesis (Birznieks *et al.* 2008).

An intriguing question to address in the future is what physiological mechanisms are responsible for such discrepancies between species and experimental approaches reported over the years? In the discussion of our article (Birznieks *et al.* 2008) we touch upon several possibilities and consider an adaptive peripheral reflex control of the fusimotor system that reflects a spectrum of function and adaptation depending on the context.

An important aspect of human experiments is voluntary control, which hypothetically might counteract nociceptive activation of α and γ-motor neurones. Apart from the fusimotor system, another less explored pathway for pain to modulate muscle spindle activity might be via the sympathetic nervous system. In our paper we review the studies advocating this possibility, but at the same time we have to point out contradictory and inconsistent findings that prevent us from drawing any definite conclusions. All previous studies have been designed to focus on either fusimotor or sympathetic influences on muscle spindles separately – a unified model taking into account of both mechanisms would probably provide a better explanation of experimental results.

While the major support to the Johansson/Sojka hypothesis has been provided by the observation of immediate reflexogenic responses, which, as we now know, are not present in humans, there is the possibility that recruitment of ©-motor neurones might require plastic changes in nociceptive circuits that might develop over a longer time. However, prolonged experimental pain in animals involving inflammatory agents seem to inhibit γ-motor neurons, thus actually providing an explanation for the weakness and even the atrophy clinically observed in severe chronic cases of muscle damage.

Finally, what about the clinical evidence – can any convincing support for the 'vicious cycle' hypothesis be found? While it is common knowledge that involuntary muscle contractions are seen in patients suffering from pain, something other than the muscle pain itself might be causing and maintaining a spasm as, for example, abdominal rigidity is associated with peritoneal inflammation. Simons & Mense (1998) indicated that usually painful muscle shows no EMG activity and, if it is present, it does not correlate with pain either in the time or intensity domain.

Furthermore, Lund *et al.* (1991) reviewed a wide range of clinical literature and experimental studies and came to the conclusion that chronic pain tends to *inhibit*, not facilitate, voluntary and reflex contractile activity of a painful muscle or its agonists. These authors suggest that those effects are beneficial and provide protective adaptation, and are definitely not the cause of pain.

In conclusion, due to the controversy and conflicting results reported over the years, a final chapter on this issue is far from being written yet.

However, now there is new direct experimental evidence indicating that the key mechanism – on which the clinical 'vicious cycle' hypothesis is based – is missing; in humans activation of muscle nociceptors does not cause a reflex increase in fusimotor drive. Thus we urge caution in extending animal data to the clinical setting.

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Movement automaticity shows less activation, but more connectivity: a model for brain efficiency

Functional MRI (fMRI) was used to investigate interactions in the brain when movements were sufficiently practiced as to become automatic. When a motor task achieved automaticity a group of brain regions became less active, but more strongly connected. Tao Wu and colleagues speculate that this increase in connectivity reflects more efficient brain function when a task is well learned

After a great deal of practice people can perform some movements automatically. Automaticity implies that movements can be performed without attention being clearly directed toward the details of the movement. Previous functional neuroimaging studies, including our own, have found that the process of automaticity is accompanied by a reduction of brain activation in several regions, like the cerebellum, premotor area (PMA) and dorso-lateral prefrontal cortex (DLPFC) (Wu *et al*. 2004; Poldrack *et al*. 2005). However, the physiology of automaticity was still far from being understood. A further obvious question that arises from these observations is how people can use less brain resources yet perform motor tasks better. We hypothesized that the acquisition of automaticity is not only related to the changes of the magnitude of neural activity, but is also associated with a modification

Tao Wu (*above*, *left*), Piu Chan (*above*) and Mark Hallett (*left*) focus on understanding motor control in normal and disorder conditions.

of the interactions within brain networks. In recent years, a great effort has been made in exploring inter-regional connectivity in a given task, which is usually characterized in terms of functional connectivity or effective connectivity (Friston *et al*. 1993). Effective connectivity implies an interaction between brain regions that might be responsible for a behavioural change. In the current study, we used functional MRI (fMRI) and effective connectivity to investigate the interactions among brain regions when movements become automatic.

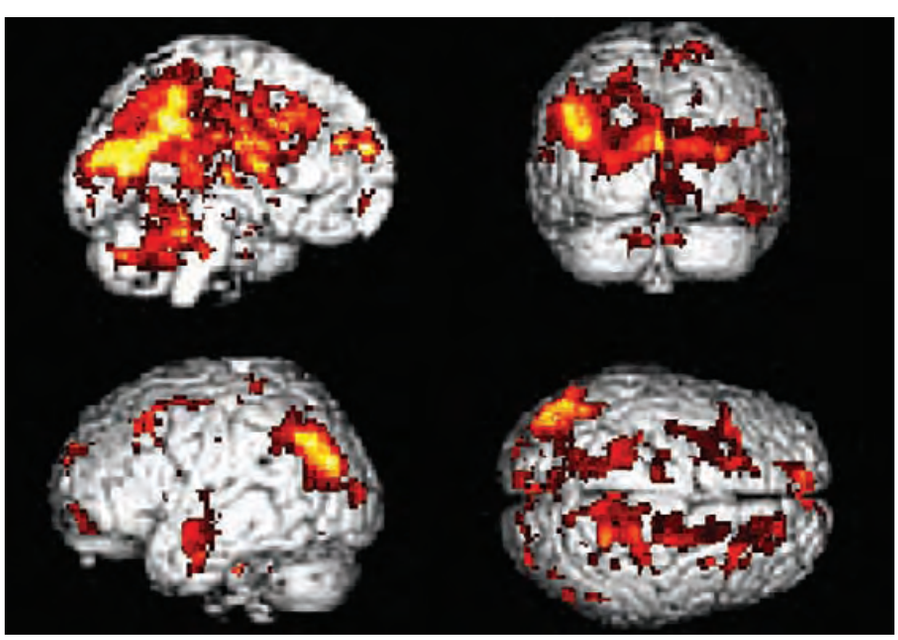

Figure 1. Results of psychophysiological interaction (PPI) from the cingulate motor area (CMA). Red colour means that these brain regions receive significantly greater influence from the CMA at the automatic stage compared to the novel stage ($p < 0.05$, corrected for multiple comparisons) (from Wu *et al*. 2008).

Healthy volunteers were asked to practice a sequential finger movement, and after extensive training they performed the task automatically. Automaticity was evaluated by having subjects perform a secondary task simultaneously with the sequential movement. No deterioration in performance indicates that the behaviour is automatic. fMRI data analysis was performed with SPM2 software (Wellcome Institute of Cognitive Neurology, London, UK). First brain activations during the novel and the automatic stage were calculated and compared. fMRI results showed that the pattern of brain activity while performing sequential movement was similar at the novel and the automatic stage, but that the bilateral cerebellum, bilateral PMAs, bilateral parietal cortex, left DLPFC, pre-supplementary motor area (pre-SMA), cingulate motor area (CMA), precuneus, and left putamen were less activated as the sequential movement became automatic. Then, automaticity-dependent changes in effective connectivity were assessed using a psychophysiological interaction (PPI) model (Friston *et al*. 1997). PPI is defined as the change in contribution of one brain area to another due to a change in experimental condition or psychological context, and aims to explain regionally specific responses in terms of the interaction between the psychological variable and the activity in a specific index area. We

Table 1. Results show brain areas that commonly receive significantly more influence from five index areas (the cerebellum bilaterally, CMA, pre-SMA, and left putamen) at the automatic stage compared to the novel stage (conjunction analysis, $p < 0.05$, corrected).

Brain area	Cluster size	Coordinates			Z-value
		x	y	z	
L anterior cingulate area	3533	-10	11	34	5.22
L precuneus	435	-16	-46	48	4.92
L parietal cortex	312	-40	-74	36	4.72
L cerebellum, posterior lobe	143	-8	-65	-27	3.94
R cerebellum, anterior lobe	89	14	-65	-25	3.88
R dorsal premotor area	61	14	-14	60	3.42
L dorsal premotor area	52	-20	-5	62	3.22

The coordinates are given as stereotaxic coordinates referring to the atlas of Talairach and Tournoux. Cluster size is the number of voxels. All areas were significant at $P < 0.05$, corrected. The z-value shows statistical difference between the automatic and novel stage. With SPM software, the z-value is determined after transformation of t-values into normal distribution. Abbreviations: L: left; R: right; CMA: cingulate motor area; SMA: supplementary motor area.

chose the left primary motor cortex (M1), bilateral dorsal PMA, bilateral DLPFC, bilateral cerebellum, left putamen, SMA, CMA, and precuneus as index areas because these regions may be involved in the process of automaticity or are important in motor learning. We found that the bilateral cerebellum, CMA, pre-SMA, and left putamen have stronger interactions with a number of brain regions at the automatic stage compared to the novel condition (Fig. 1 and Table 1). In contrast, the precuneus has decreased effective connectivity at the automatic stage.

These findings suggest that the process of automaticity is accompanied by a strengthened interaction within much of the central motor networks even though the magnitude of the activation is decreased. With automaticity, brain regions become less active, but some of them increase their effective connectivity. If a movement becomes automatic, then learning must occur, and thus synaptic strengths must change. These changes appear to allow the brain to function more efficiently for the given task, even with a reduced level of activation. The network that does become more connected includes the basal ganglia and cerebellum. In contrast, some cortical regions, like the DLPFC, PMA, and M1, did not show stronger automaticity-related effective connectivity. The primary motor cortex itself is not a part of the automatic networks, perhaps indicating that at this stage it is acting largely in execution mode, carrying out the directions sent to it. The result showing the decreased connectivity of the precuneus can be interpreted that the importance of the cortical attention network decreases when movements become automatic. These findings taken all together provide evidence for the previously poorly supported, but widely held, view that the execution of automatic movements is shifted more subcortically.

The brain is constantly learning new things, but cannot continuously increase its activity. Increasing the functional strength of connections is a solution to this problem and may be an important generalizable property of brain function.

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Paton Prize Bursary

The Paton Prize was established in 1994 by The Society's History & Archives Committee to encourage the study of the major ideas and concepts that have shaped modern physiology. The Prize takes the form of a bursary to support such studies, with funding of up to £1000 to cover travel and incidental expenses. The Committee wishes to promote interest in the history of physiology among younger Members and Affiliates of The Society, as well as established scientists.

The bursaries are financed by interest from the Paton Fund, an endowment originated by a donation from Sir William Paton, with a matching donation from The Society.

For more information on the Paton Prize Bursary, or to suggest a future recipient, please contact the Committee Chair, Dafydd Walters (dwalters@sgul.ac.uk)

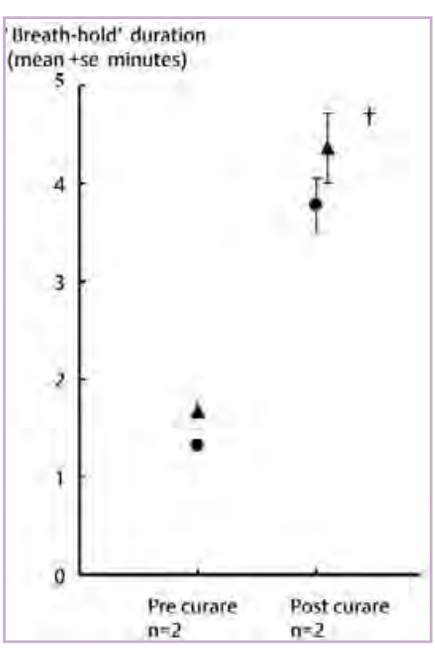
So what does cause the breakpoint of breath-holding?

The precise mechanism causing the breakpoint of breath-holding is unknown, but it is possible that breath-holding eventually stimulates diaphragm chemoreceptors that in turn cause the irresistible urge to breathe

It is not normally possible for humans to breath-hold voluntarily until they lose consciousness (Parkes, 2006). This indicates that the voluntary act of breath-holding is terminated by some involuntary breakpoint mechanism. The nature of this involuntary breakpoint mechanism might be revealed by the three well known manoeuvres that prolong breath-hold duration:

- increasing lung inflation;
- breathing hyperoxic gas mixtures;
- lowering arterial PCO_2 by previously hyperventilating.

These three suggest that the breakpoint mechanism might involve pulmonary stretch receptors and/or the carotid arterial chemoreceptors (not aortic chemoreceptors as these have no effect on breathing in humans). This in turn predicts that humans should be able to breath-hold indefinitively (until consciousness is lost) after pulmonary or carotid chemoreceptor denervation. Such denervation however has almost no effect on breath-hold duration (see Harty *et al.* 1996; Flume *et al.* 1996; Gross *et al.* 1976, in Parkes, 2006). So pulmonary stretch and carotid



Michael Parkes.

chemoreceptors are not obviously involved (although any proposed mechanism must still explain such prolongations).

There are three other, and less well known, manoeuvres that also prolong breath-hold duration and that might also reveal the breakpoint mechanism. The first appears to be voluntarily relaxing the diaphragm at the end of the breath-hold. Fowler (1954, in Parkes, 2006) made one of the earliest observations consistent with this (subsequently confirmed by Flume *et al.* 1994, in Parkes, 2006), by showing that inhaling an asphyxiating gas mixture at breakpoint enables a second (or even third) breath-hold, despite blood gas levels becoming progressively worse. This enabling effect is independent of the number of inhalations of asphyxiating gas, occurs even with a single inhalation with no net change in lung volume, or even apparently if inspiration is only attempted against a closed glottis (Rigg *et al.* 1974, in Parkes, 2006). Their one common feature might be in momentarily relaxing the diaphragm before using it to attempt to inspire again.

Figure 1. Mean 'breath-hold' duration with 70% oxygen in two subjects pre- (from FRC) and post-curarisation. Separate symbols indicate each subject. †The anaesthetist terminated the 'breath-hold' by restarting the ventilator. Reproduced from Campbell *et al.*(1966) with permission from the *Lancet* (*pending*) [& see also Campbell *et al.* 1967 & 1969, in Parkes, 2006].

This in turn suggests that the 'holding' of breath-holding might be achieved by continuously contracting the diaphragm slightly (Parkes, 2006), with the purpose of opposing the recoil from the chest. (It may be easier to oppose this recoil by slightly activating a big inspiratory muscle like the diaphragm rather than by intensely activating a small group of muscles such those keeping the glottis closed. Substantial diaphragm proprioreception is also unlikely as humans have little conscious sensation of the diaphragm).

During breath-holding such an unusual, prolonged diaphragm contraction may eventually result in under perfusion of the diaphragm, causing a stimulation of diaphragm muscle chemoreceptors that eventually generates the irresistible urge to breathe, i.e. the breakpoint of breath-holding. Stopping breath-holding by relaxing the diaphragm may then allow it to be reperfused, ending the stimulation of diaphragm chemoreceptors by metabolites. This hypothesis could explain the prolongation of breath-hold duration by increased lung inflation, hyperoxia and hypocapnia, with each delaying the onset of such diaphragm chemoreceptor stimulation. Even if diaphragm chemoreceptor stimulation is only perceived vaguely as discomfort, the ability to tolerate such discomfort will have a strong subjective component that could also explain the notorious variations in breath-hold duration seen both between and within subjects (Parkes, 2006).

This key role of the diaphragm in the breakpoint mechanism (Parkes, 2006) is supported by the second less well known breath-hold prolonging manoeuvre, paralysis

(curarisation) of the diaphragm. In 1966–1969 Campbell *et al.* described two conscious, unanaesthetised subjects whose entire voluntarily (skeletal) musculature was paralysed with curare (except for one arm left intact so that the subject could make hand signals) and who were kept alive by mechanical ventilation. Turning off the ventilator did not induce any intense feeling of suffocation, nor distress, nor any urge to breathe. Fig. 1 shows that the two subjects remained unventilated for as long as the supervising anaesthetist permitted (about 4 minutes, when arterial PCO_2 had reached ~72 mmHg) i.e. 'breath-hold' duration was apparently prolonged indefinitely.

Is the mechanism explaining this astonishing observation simply curare preventing the diaphragm from contracting and hence its blood flow is never restricted sufficiently to activate diaphragm chemo-receptors? Unfortunately, the results of this intriguing and alarming experiment have not yet been confirmed. The one attempt to do so (Gandevia *et al.* 1993) was unsuccessful, but may be inconclusive since the three subjects apparently had had enough before their PCO_2 levels had even risen above normal levels (43 mmHg).

Most of Campbell's results are, however, confirmed in a related experiment. Noble *et al.*(1970) locally anaesthetised the phrenic nerves bilaterally in three subjects. Such anaesthesia blocks the well known motor efferents to the diaphragm. It also blocks the rarely considered but extensive sensory afferents in the phrenic nerve that include those from diaphragm muscle chemoreceptors (Parkes, 2006). Blocking either would result in the loss of afferent activity from diaphragm chemoreceptors. Fig. 2*A* shows that Noble *et al.* (1970) confirmed a prolongation (doubling) of breath-hold duration.

Unfortunately these experiments, too, are now ethically unrepeatable. So it is unclear whether their failure

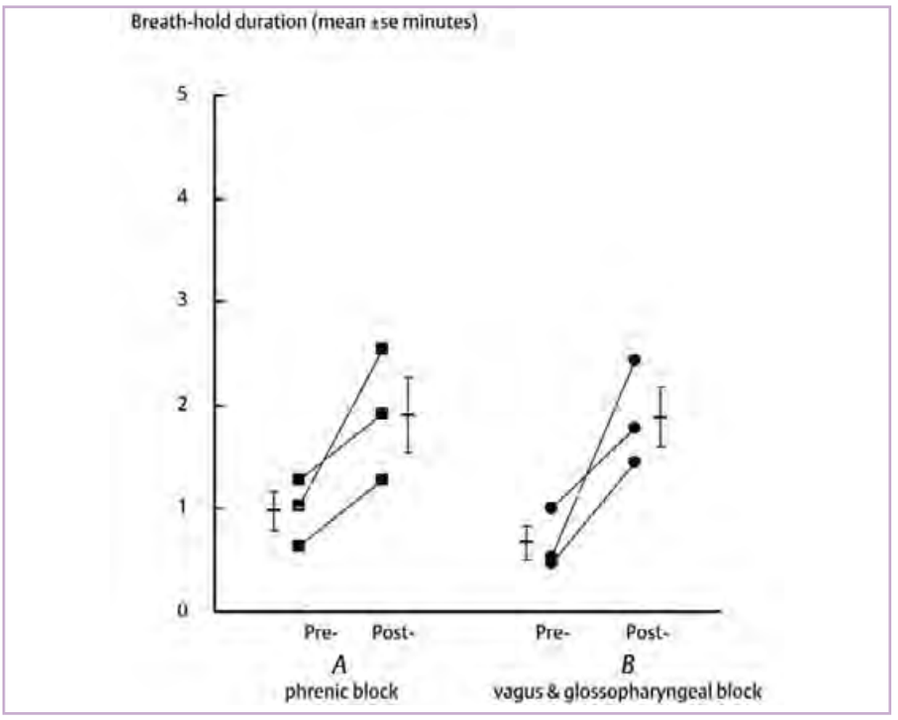


Figure 2. Prolongation of breath-hold duration by *A*, bilateral phrenic block (reproduced with permission from Noble *et al.* [1970 & 1971, see Parkes, 2006], the Novartis Foundation, *Clinical Science*, © the Biochemical Society, the Medical Research Society and Wiley-Blackwell. *B*, bilateral vagus and glossopharyngeal nerve block (reproduced with permission from Noble *et al.* [1970], the Novartis Foundation and Wiley-Blackwell) (and see also Guz *et al.* 1966; Guz,1966, in Parkes, 2006). Note breath-holds were at end expiration (FRC). They were from 100% O_2 for *A* (Noble *et al.*1971, in Parkes, 2006) and apparently mostly from 100% O_2 for *B* (Guz *et al.*1966; Guz,1966; Noble *et al.*1970, see Parkes, 2006). Squares & circles indicate individual subjects with the mean ±se for each pre and post block condition indicated as horizontal bars.

to confirm Campbell's indefinite 'breath-hold' duration is due to incomplete blockade of phrenic motor efferents and or sensory afferents, or that Campbell's result is indeed unconfirmable.

The third less well known breath-hold prolonging manoeuvre is the demonstration (Fig. 2*B*) by Noble *et al.* (1970) (now also ethically unrepeatable) that bilateral local anaesthesia of the vagus and glossopharyngeal nerves prolongs (almost trebles) breath-hold duration. The precise afferents involved are unclear, but must involve blockade of non-pulmonary afferents (because pulmonary denervation itself has no effect on breath-hold duration (Flume *et al.* 1996; Harty *et al.* 1996, in Parkes, 2006) and blockade of non-carotid and non-aortic chemoreceptor afferents (because carotid denervation itself has no effect on breath-hold duration under similar hyperoxic conditions (Gross *et al.*1976, in Parkes, 2006) and aortic chemoreceptors have no effect on breathing in humans).

The breath-hold prolonging effects of diaphragm paralysis, phrenic and vagus with glossopharyngeal nerve blockade could be combined in the radical suggestion (Parkes, 2006) that diaphragm afferents might travel partly with or within the vagus nerves. This idea is not without precedent, since the vagus and phrenic nerves are sometimes in close proximity and the phrenic nerve in dogs does contains abdominal and thoracic afferents from the heart and vena cava (Kostreva & Pontus, 1993a; Kostreva & Pontus, 1993b).

Clearly the hypothesis that diaphragm chemoreceptors play a role on the breakpoint of breath-

holding is still largely speculative. During breath-holding in man we still know almost nothing about diaphragm activity, nor its perfusion nor its chemoreceptor activity. Perhaps the latest developments in imaging will rekindle some interest in studying the mechanism explaining the breakpoint of breath-holding in man?

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Animals in research: make up your own mind

The Physiological Society, in collaboration with GlaxoSmithKline, the Coalition for Medical Progress and the Biomedical Research Education Trust, launched an educational DVD aimed at 14 to 16 year olds, which is now available online. The content, includes a 19 minute film, featuring patients, researchers, doctors and vets, explaining why and how animals are used in medical research. Also included are two supplementary filmed case-study modules on coronary heart disease and malaria, plus teachers' resource materials and sources of further information from all sides of the debate.

To view the DVD online visit Education resources at http://www.physoc.org. For copies of the DVD email ebell@physoc.org.

Olfactory marker protein: a gift to molecular biologists, an enigma to physiologists

Olfactory marker protein (OMP), a small cytoplasmic protein almost exclusively expressed in nasal chemosensory cells, has made major contributions to research progress in olfaction ever since its discovery over 35 years ago. However, the function of OMP and its mechanism of action has remained an enigma. Slowly, answers to these questions are beginning to emerge

Everyone working in the field of chemosensation knows OMP, but nobody knows its function. A PubMed search for 'olfactory marker protein' yields around 350 publications, but when probing deeper to identify what OMP does physiologically at the cellular or molecular level, this number drops to single digits. Antibodies to OMP have been used to characterize olfactory receptor neurons (ORNs) in numerous species and the OMP gene has been used to generate transgenic mice with ORN-specific expression profiles in hundreds of publications. However, to date only one protein has been identified that interacts with OMP, and that might provide insight to help elucidate OMP's function. So why is OMP so widely utilized, while so little is known about its function?

Johannes Reisert (*left*) and Frank Margolis.

OMP is a small (~160 amino acids) cytoplasmic protein (Margolis, 1972). Its amino acid sequence is >50 % identical in all vertebrate species but has no known sequence motifs. OMP is abundantly and virtually exclusively expressed in mature chemosensory neurons in

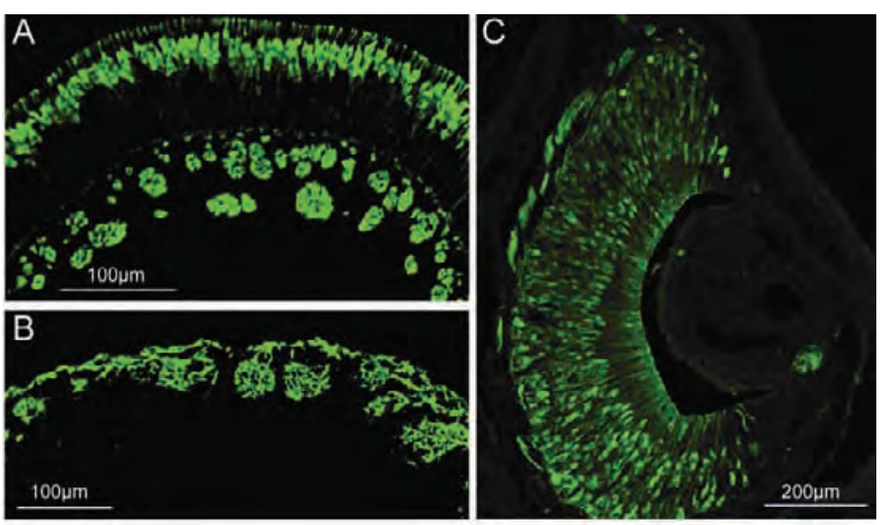

Figure 1. Distribution of OMP in coronal sections of the mouse olfactory system visualized by immunofluorescence staining and confocal laser scanning microscopy at P7. *A*, Olfactory epithelium: cell bodies of mature ORNs occupy the upper third of the epithelium and are intensely stained, as are their dendrites and dendritic knobs at the surface of the epithelium. ORN axon bundles are apparent in the sub-epithelium as stained circular objects. At this age immature ORNs deeper in the epithelium do not express OMP. *B*, Olfactory bulb : The axon bundles project to the olfactory bulb glomeruli seen just below the surface of the bulb where the ORN axons enter. *C*, Vomeronasal organ: sensory neurons in the sensory epithelium of the VNO are seen to stain for OMP and their stained axons exit superficially, while the non-sensory portion of the VNO is devoid of staining (with the possible exception of one ectopic cell).

the nasal cavity (Fig. 1). As such OMP has been a valued and cleverly exploited tool to identify and label vomeronasal and ORNs, neurons of the septal organ and also contributed to the recent rediscovery of the Grueneberg ganglion, a cluster of cells located in the anterior nasal cavity. Furthermore, the OMP promoter or the OMP locus has been used extensively to drive expression of desired genes in chemosensory neurons. Examples are the markers thy1.1, lac-Z or GFP, which have helped to describe fundamental connectivity patterns of olfactory receptor neuron axons to their glomerular targets in the olfactory bulb (e.g. Danciger *et al.* 1989; Mombaerts *et al.* 1996), direct expression of a single identified olfactory receptor to every ORN (instead of a randomly chosen one), or expression of the fluorescent exocytosis indicator synaptopHluorin to image bulbar activity patterns (Bozza *et al.* 2004).

Table 1. Indications of biological function of OMP

- OMP induces increased mitotic activity of ORN precursors
- A prolonged developmental delay in ORN axon retraction from bulbar glomeruli is observed in $OMP^{-/-}$ mice
- OMP interacts with Bex 1 and 2 proteins that can bind Ca/CaM
- $OMP^{-/-}$ ORNs have a reduced ability to extrude Ca^{2+} from ORN knobs
- $OMP^{-/-}$ ORNs have prolonged cAMP kinetics in ORN cilia
- $OMP^{-/-}$ ORNs exhibit delayed onset and offset of odourant electroolfactrogram responses
- $OMP^{-/-}$ ORNs have unaltered axonal conductance velocity
- Odour detection in $OMP^{-/-}$ mice requires a 50-100x higher concentration
- $OMP^{-/-}$ mice have altered epithelial odourant response patterns monitored with voltage sensitive dyes.

(Relevant references to these reports are found in Reisert *et al*. 2007)

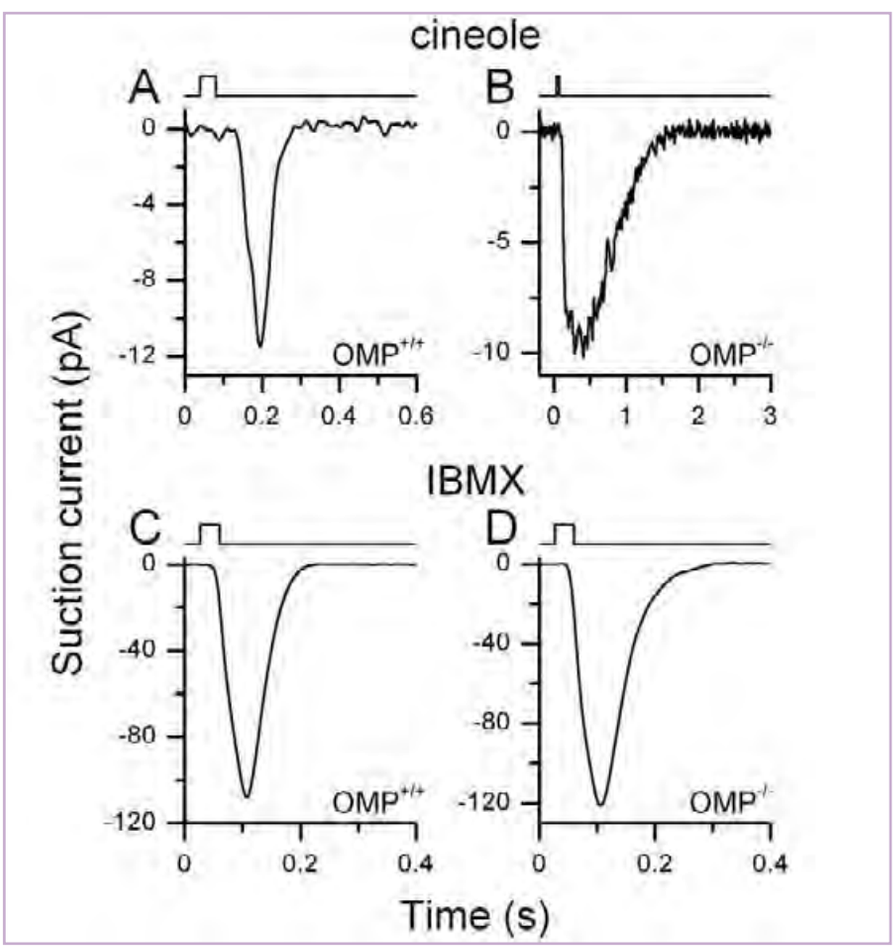

Figure 2. Suction pipette recordings from wildtype, *A*, and $OMP^{-/-}$, *B*, olfactory receptor neurons, which were stimulated with the odorant cineole as indicated by the solution monitor above the recordings. Note the compressed time scale in *B* and the severely prolonged termination phase of the response. Such a prolongation was not observed in $OMP^{-/-}$ ORNs when the phosphodiestease inhibitor IBMX was used to stimulate (*C* & *D* wildtype and $OMP^{-/-}$ ORNs respectively). This stimulation paradigm 'shortcuts' early stages in olfactory signal transduction, indicating OMP acts on those early transduction steps. Modified from (Reisert *et al.* 2007).

Not until the generation of an OMP knockout (Buiakova *et al.* 1996) was it actually certain that OMP has a role in olfactory transduction (see Table 1 for biological functions of OMP). Immunohistochemical and anatomical analyses of $OMP^{-/-}$ olfactory epithelium revealed no differences in morphology or protein expression, suggesting that OMP may not play a developmental role.

Interestingly, $OMP^{-/-}$ ORN axons are compromised in their ability to properly target the correct glomerulus in the bulb (St John & Key, 2005). In addition, the olfactory bulbs of $OMP^{-/-}$ mice are smaller and display reduced tyrosine hydroxylase activity and CCK content, changes also observed in bulbs of odour-deprived wild-type mice. These observations imply that OMP alters afferent input to the bulb by modulating the activity of ORNs, which is indeed the case. The odour-induced electrolfactogram, a mass epithelial recording, revealed that ORNs which lack OMP have a response, where not a single, but at least three aspects are slowed: response delay, time to peak and the response termination (Buiakova *et al*. 1996). Single cell recordings confirmed these findings and also revealed that odour-induced action potential patterns were changed (Fig. 2). Action potentials were generated with a 3-fold longer delay after stimulation onset and firing persisted for longer compared to wild-type recordings (Reisert *et al*.

2007), both possibly contributing to the bulbar changes observed in OMP knockouts. $OMP^{-/-}$ ORNs also showed a severely reduced ability to recover from adaptation due to the 10-fold slowed termination of the receptor current, an effect which might also contribute to the observed 50-fold reduction in odour sensitivity of $OMP^{-/-}$ mice when tested behaviourally (Youngentob & Margolis, 1999).

These dramatic and multiple effects of OMP on the odour response suggest that it must function at a regulatory focal point in ciliary olfactory transduction. In ORNs activation of an odorant receptor leads, via a G protein, to adenylyl cyclase activation, increase in ciliary cAMP and activation of a Ca^{2+} permeable cyclic nucleotide-gated (CNG) channel, followed by opening of an excitatory Ca^{2+}-activated Cl^- channel. Response termination occurs by degradation of cAMP by a CaM-dependent phosphodiesterase and removal of Ca^{2+} by a Na^+/Ca^{2+} exchanger and PMCA activity to close the CNG and the Cl^- channel respectively. On which or on how many transduction components might OMP exert its effect? cAMP kinetics have been found to be greatly prolonged in $OMP^{-/-}$ ORNs suggesting that either cAMP production itself is prolonged or degradation slowed. The former is the case, suggesting that the action of OMP in the cilia may be restricted to the early stages of signal transduction prior to cAMP production: the odorant receptor, G protein and/or the adenylyl cyclase (Reisert *et al.* 2007). Hence OMP's role is to speed up the odorant response, which might contribute to fast sampling of odour cues and allowing ORNs to re-sensitize quickly. This is consistent with the alterations in odorant-induced mucosal activity patterns in $OMP^{-/-}$ mice (Youngentob *et al.* 2003).

Nevertheless, many questions remain. Does OMP act *directly* on the previously mentioned transduction components? Probably not, since vomeronasal neurons also express OMP but use an entirely different PLC based-transduction pathway. Similarly OMP positive cells of the Grueneberg ganglion express, besides odorant receptors, trace amine-associated and vomeronasal receptors. This implies the presence of a protein common to all OMP-expressing cells through which OMP exerts its function on a range of quite different transduction components. A possible candidate might be members of the family of brain expressed X-linked (Bex) genes which have been found to interact with OMP and to be present in ORNs of the main and vomeronasal epithelium (Koo *et al.* 2005).

On the other hand, if OMP is truly a more general modulator of signal transduction cascades, why is its expression so highly restricted to nasal chemosensory neurons, but not to other (e.g. chemosensory taste or gut) cells? The absence of OMP orthologs in invertebrates suggests that it is not required *per se* for chemosensory detection. Furthermore it can also not be assumed that OMP only has a role in chemosensory signal transduction, since it does not localize exclusively to the cilia or vomeronasal microvilli, but is present throughout the entire cell.

Hopefully, in the coming years, OMP will become less of an enigma and more of a gift to physiologists too by revealing its function and providing new insights into signal transduction mechanisms.

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Icelandic banking crisis: impact on The Society

Further to earlier reports on The Society's website, I can confirm that £523k deposits held with Kaupthing Singer and Friedlander will be guranteed in full by the Financial Services Compensation Scheme (FSCS).

The Society has received and returned a compensation claim form which will be processed by the FSCS in due course.

Casey Early
Finance Manager

Openness and animal research: are you doing enough?

There has been a noticeable shift towards more openness on the issue of animal research. In the last few years we have seen more universities post policy statements on their websites and an increasing number of scientists now feel comfortable to discuss the animal research aspect of their work more openly.

This shift did not happen overnight. Animal rights extremism, the reason most often quoted by those who are hesitant to being open, is on the decline. The media have not only turned against extremists and their tactics but are now interested in reporting science accurately, therefore allowing the public to understand the scientific process better.

In the past 2 years, the Research Defence Society (RDS) has been spreading the good news and encouraging academic institutions to become more open about animal research.

So what do we mean by being open? Many scientists and administrators across a number of academic institutions still remember stories they have heard about scientists being targeted at their own homes or being inconvenienced and harassed on a daily basis at their places of work. It comes as no surprise then that a lot of people have told us that 'they don't want to advertise the fact that they do animal research' and would much rather stay 'below the extremists' radar'. But this degree of fear is no longer necessary. Recent evidence shows that, thanks to robust police response and new legislation that curtails extremist activity, individual scientists are no longer targeted.

In addition, not all those who oppose animal research engage in extremist activities, in fact the extremists are just a minority. Indeed anti-vivisectionist groups use communications to make their case to the public, not intimidation.

Animal research is not a secret to those who oppose it. Scientists publish in peer review journals and present their work at conferences. Those who oppose animal research know this and regularly search journals for articles.

What's more, being open about this issue is not about advertising it. It is about communicating the animal research aspect of your research in all of your communications activities, whether that is with the media, a group of school children, members of your local community and politicians. Indeed, the same people that those who oppose animal research are trying to reach.

There is a long list of activities individual scientists and institutions can carry out as part of being open. Our experience in the past 2 years, however, has shown that in order to achieve significant change it is important that there is institutional commitment on the issue. This is the only way to ensure consistency in communications which will ultimately work towards gaining more public support and creating better understanding for animal research.

The individual drivers for institutional commitment may vary from an enthusiastic scientist to an equally enthusiastic press officer. What's important is to bring a group of decision makers together who will agree on the way forward for the institution and identify the steps they can take to achieve transparency and openness without provoking those who are sensitive on the issue.

If you think that your institution should be making considered steps towards more openness and would like advice and support please contact me (corinah@rds-net.org.uk / 020 7478 4387).

Corina Hadjiodysseos
Communications and Public Affairs Manager, RDS

As of December 2008, the Research Defence Society (RDS) will merge with its sister organisation Coalition for Medical Progress (CMP) to create a new organisation called Understanding Animal Research, which will build on the strengths of both. This was the conclusion of a review by a working party of stakeholders in the Summer of 2008. The work of RDS on openness has been endorsed by the review committee and will continue as an integral part of the activities of Understanding Animal Research.

AnimalResearch.info

Scientists and researchers are needed to contribute to a new website on the use of animals in research

AnimalResearch.info, a new website about the use of animals in research, invites Members of The Physiological Society to share their knowledge and experience of the research process with a wider audience. The website allows scientists to contribute content directly, putting sound information on animal research into the public domain. If you are interested in making additions to the site you can register at www.AnimalResearch.info.

The site has been developed by RDS, in collaboration with like-minded organisations worldwide, to provide a source of authoritative information about the scientific and medical benefits of animal research. Its wiki-format allows contributions to be made easily by scientists. The articles show how and why particular methodologies are used, ultimately providing a rationale for your research.

Designed with journalists and researchers in mind, most of AnimalResearch.info's content is presented in a list format, which can be easily searched and sorted. The site is written for non-specialists, but is referenced and provides links to

more technical information and expert sources. An editorial, review and validation process ensures that only registered specialists can contribute, keeping the information on the site clear and credible. The aim is to give scientists a voice and to give non-scientists a better understanding of scientific research.

The content includes summaries of the animal experiments which led to Nobel Prize winning discoveries, details of how particular animal models are used to study aspects of basic and applied research and general articles or lectures that show how animals have contributed to medical knowledge. Contributions such as further concise summaries that show why a particular animal model is suited to an experiment or area of research are especially welcome.

Those who work with animals often find it difficult to speak about their research beyond scientific circles. The new website now gives scientists an opportunity to be more open about their work, sharing the rationale for their research with a wider audience. With your support, we hope that AnimalResearch.info will become the ultimate source of expertise in this area.

To view the current content, register as a contributor, or make suggestions for improvements, visit www.AnimalResearch.info. For further information please contact info@animalresearch.info.

Physiology News

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

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

(Sa)tired out?

It is a fair while since I have been here, but current chief satirist Keith Cormorant seems to be on vacation (satirical sabbatical?). Or perhaps he just needed a rest. Anyway, they asked if I would return and fill in.

People sometimes ask why I stopped writing the *Unbelievable!* column. The main answer is that I ran out of satirical gas, or more accurately out of subjects to be satirical about. I sometimes think each budding satirist only has a certain number of satirical articles, or subjects of such, in them. Once you have written about all of these subjects, you can either re-cycle the same themes over and over (a method favoured by many national newspaper columnists) or you can simply admit that you have 'dried' and that it is time to quit the stage.

A different reason sometimes given by satirists for retiring is that reality itself has gone beyond satire. As I write this, one of the two US political parties has nominated a candidate for the Vice Presidency, Sarah Palin, who believes in *intelligent design* rather than evolution by natural selection. She has also been reported to believe in witches, that dinosaurs and people co-existed not that long ago, and perhaps that the earth is only 6000 years old. This in the 21st century.

And by the time you read this, she may even be Vice President. I do struggle to see how satire can compete with that.

This view is not original to me, of course. The great American musical satirist Tom Lehrer made the same point back in the mid 70s, after the Nobel Committee awarded the 1973 Peace Prize to Henry Kissinger and Le Duc Tho, two noted exponents of war and *Realpolitik*. Since Dr Kissinger had been heavily involved in one the 20th century's greatest bombing campaigns – the 'carpet-bombing' of Cambodia, a country the US was not even at war with at the time – the 1973 Peace Prize award was – how shall I put this? – imaginative in concept. As Lehrer said, it was hard to know where you could go with satire when real life events exceeded, in parodic power, anything one could dream up as a mere parody.

Occasionally, satirists have a different - though not altogether pleasant - experience, when something they wrote as a parody later actually *becomes* a reality. This happened to one Professor of Physiology I know, who penned a column some years ago in this very slot[1] where he was quite uncomplimentary about assessing peoples' research by citation counting and metrics. To emphasize just how ridiculous it was, he satirically suggested creating an index called the *Centrifugal Factor* – a number that quantified an author's degree of credit for a paper based on his or her position in the author order. The nearer to the outer ends of the paper the author came – the nearer to either first or last authorship – the higher the *CF*, and the more points the author scored.

Imagine my friend's consternation a few years later when Imperial College was reported (notably in these pages by David Colquhoun[2]) to be using this precise method in computing 'research output metrics' for their staff.

As they say: you couldn't make it up.

So, after all that gloom, is satire dead? Well, despite the above gloom, hopefully not – at least as long as there are satirists, or subject matter. And both of these do seem to renew themselves, despite the problems of parodic reality and personal satirical atrophy. Individual satirists come and go, but satire seems to keep going.

However, if there is one thing *all* satirists are agreed on, it is that is that we never have enough ideas.

Which is where you come in.

The inspiration-starved satirists here at *Physiology News* are keen to hear *your* ideas for subjects for satirical columns. So all ideas, please, or accounts of things that have happened to you that are crying out to be parodied, to the Executive Editor[3].

We promise only to steal the good ones.

Mark Cain

Notes

1 Anon (2005). Unbelievable! *Physiology News* **58**, 50.
2 Colquhoun D (2007). How to get good science? *Physiology News* **69**, 12–14.
3 Email (lrimmer@physoc.org) under a pseudonym if you prefer – I recommend an anonymous Gmail account – will be fine.

Hands on science in schools

Chrissy Stokes and I went along to this Parliamentary and Scientific Committee seminar on 22 April, chaired by Douglas Naysmith MP. The future of physiology to some extent depends on children being enthused by science in school, and getting a good grounding in practical science skills. Our Society has become very concerned in the last few years about how this may be becoming neglected in schools, so we were keen to hear what they had to say. The seminar was addressed by Tina Overton (Higher Education Academy/Department of Chemistry, University of Hull), Karen Bultitude (Science Communications Unit, University of the West of England) and Hugh Cartwright (Department of Chemistry, University of Oxford).

The main points that struck us from the discussion were as follows.

A HEFCE report in 2005 resulted in the Secretary of State identifying STEM disciplines as being vulnerable, in particular the high profile closure of some university departments. Even the biosciences are vulnerable if you exclude currently popular subjects such as sports sciences. The situation is stark when you consider that the higher education sector has quadrupled in the last few years, so our STEM 'market share' has plummeted. Recruitment of science students has not been helped by a crisis in science teaching in schools, with the core science subjects increasingly not being taught by their subject area specialists. Good science role models in schools are essential, reinforced by good careers advice. Some efforts are being made to tackle this, including giving 'golden hellos' to science graduates to enter the teaching profession. Science Learning Centres are there to try to give support to teachers, but an issue is that they have to charge for courses, and need teachers to be released from their duties, making participation a difficult issue for under-resourced schools.

Various initiatives now exist to try to promote practical science teaching. These include an EU funded scheme, *Hands on science*, various Higher Education Funding Council projects (e.g. *Chemistry: the next generation*). Often these initiatives are mainly about curriculum enrichment, but they are becoming increasingly 'whizz bang', hands on, and trying to attract potential students to local universities. Important aims are enhancement and enrichment, such initiatives need to enhance what teachers are already doing. Projects include *Robocop junior, Awesome athletics* and *Meet the gene machine* (which uses drama to stimulate debate). There was a strong consensus that the best way for children to learn is through doing experiments. Practical science initiatives need to enthuse by taking a cross-curricular approach whilst being closely linked to curriculum requirements, to be interactive and participatory, build on existing networks, acknowledge that teaching time is precious, be realistic about equipment needs and availability, and be good at reaching disadvantaged kids.

This support for all things to do with *Hands on science*, led to a very lively debate at the seminar, when Hugh discussed the potential contribution of *Hands off science* to the issue, by providing remote access to experiments in schools. This has the advantage of giving children access to experiments that could not be done within a school environment, such as looking at materials under very high resolution, access to telescopes and monitoring remote environments such as Mount Everest, and getting around various Health and Safety issues. It is hoped that such initiatives will also foster interest in collaborative, and international research, and enhance science provision at poorly funded institutions. There are important implementation issues, such as schools needing good IT knowledge and equipment to access such programmes, and the available commercial software often has many shortcomings. The subsequent debate showed people's concerns that resource problems in schools might lead to teachers favouring remote resources over the more 'hands on' stuff, but it was generally agreed that all sorts of resources and opportunities should be made available wherever possible, as our over-riding concern is to get kids to study science.

I had the opportunity in the debate to flag the existence of our Bristol colleagues' *Lab on a lorry*, which takes physiology experiments around schools and other venues. This was felt by participants to be an excellent initiative, and I suggested that Government should fund the creation of lorries to support teaching in other STEM disciplines.

Liz Bell

Should it be illegal to sell genetic tests except through a doctor?

This energetic and topical Wellcome Debate on 10 July with the general public included presentations from Christine Patch (Consultant Genetic Counsellor, Guy's/St Thomas's Hospital), Kari Stefansson (Managing Director, deCODE Genetics), Alison Stewart (Principal Associate, Public Health and Genomics Fdn) and Mark Henderson (Science Editor, *The Times*). It was facilitated/refereed by Toby Murcott (science writer/broadcaster).

The session started with Henderson sharing his experiences of buying an off-the-shelf genetic profile of himself. It gave him a lot of useful statistical information, but held no great surprises from what he was expecting from his own knowledge of his family history. An issue was how much use this additional statistical information would be in the average 10 minute consultation with a family GP.

The other presenters then shared strikingly similar perspectives on the issue. There was a general feeling that independent genetic testing should not be illegal, but should be better controlled. Real harm can result when such activities are driven into the illegal sphere as patients will always be tempted to access such tests, if need be via the internet from countries that do not have strict controls. Benefit or harm depends very much on the context in which it is used, and can include false re-assurance, causing anxiety (including to other family members who have not taken the test) and inappropriate and expensive healthcare follow up. Genetic tests can be particularly useful in identifying health issues not obvious from an individual's family history. Results need interpretation for the patients, as well as basic analysis, and people facing risk of serious disease need specific counselling. People often find it difficult to understand the difference between relative risk and an individual's personal absolute risk of suffering from any disease. From an ethical standpoint, there is a general view in Europe that children should not be tested for adult diseases, but sometimes this is essential where some diseases need to be diagnosed early for effective treatment.

To ensure good standards we need to know that reputable labs are conducting the tests, that the efficacy of tests is based on good peer reviewed evidence, that people skilled in interpreting the results are involved, that we control who has access to the results, and that there is proper follow up. Ways of getting redress if things go wrong also need to be clear. Companies should be allowed to market their products direct to the consumer but be held to high technical and other standards. Thus an outright ban is not the right way to go, but there is a policy and regulatory gap, and the healthcare professions need to be more closely involved as gatekeepers and intermediaries. This needs to be addressed to prevent possible scandals leading to public loss of confidence and the inhibition of future developments. More could probably be done using existing consumer protection legislation. A public funded healthcare system is vital to prevent financial incentives leading to misuse of results. More public funding for tests should also be considered to prevent potential 'ghettoisation' of the poor in terms of access.

It was also felt that genetic tests were part and parcel of a new relationship between patients and the healthcare professions. Patients now actively seek information on their conditions, and expect to be directly involved in the processes of diagnosis and treatment. There is also a bigger emphasis on preventative health management with people expecting to manage actively their own health. Tests are enabling a more pro-active approach to managing potential illnesses, are already saving lives and can be expected to dramatically alter our existing, largely reactive, healthcare system. Policy makers will need to pay particular attention to the impact on the insurance industry, and consider how far tests for specific issues should be allowed to undermine the long established insurance principle of spreading risks by distributing them across the population.

Liz Bell

Engaging young people with science

How, why and when?

The Science Council guest lecture was given on 13 June by Jonathan Osborne (Professor of Science Education, King's College London). His research interests include how to develop students' understanding of the nature of science, exploring what scientists and science educators should be taught about the nature of science and a major ESRC funded project exploring *Science careers and aspirations: age 10–14*. I found his talk very thought provoking.

Some of the key points I took home included the mixed messages we are getting on whether the state of school science education in the UK is a problem. Governments around the world are very worried about this issue, with various pessimistic reports about the future supply of scientists. However, the situation may not be as bad as people fear. The number of A Level students taking chemistry and biology will hit current Government targets, although physics is a problem. In the USA, the supply of biomedical PhDs aged 35 or younger has increased by 50%, but the number of tenured positions available remains flat and the unemployment statistics indicate that there is no real shortage of people in general. Some specific areas, such as maths and pharmacology, may have problems. Science is now a global endeavour, with people routinely being recruited to fill positions from other countries, so the future of science is not just dependent on engaging the interest of local school children.

Various surveys have noted that in developed countries, students seem generally less interested in studying science than in the developing world, particularly the girls. So how do we engage them? Girls seem to prefer subjects showing the social relevance of science, for example cancer, boys preferring more gung-ho subjects such as atom bombs, and traditional approaches to teaching solid blocks of physics, chemistry and biology only seem to work for a minority of 14–16 year olds. Evidence shows that if you are going to interest young people, you need to grab their attention before age 14, after that

they have already started shutting their mental doors on potential careers. Success in maths at schools also strongly influences people's interest in taking up areas such as physics, but does not correlate so strongly in decisions to study life sciences.

There may also be issues with current teaching approaches, with too much emphasis on the recall of facts rather than facilitating understanding, an over-reliance on 'transmission' making it seem authoritative and boring, too much copying and repetition, and lack of space for genuine discussion. Attracting and engaging are more important than force-feeding facts. There may be a particular problem in primary schools where there is too much focus on testing kids. The danger here is that the brightest kids will not see science as an intellectual challenge. Additional problems include lack of adequate careers advice, problems in recruiting enough science teachers to fill vacancies, and making sure that the science teachers we do have are well informed.

He concluded by painting a vision of what science education should look like in the future. To engage more children's interest, we need to address the needs of the non-scientist, and promote a broader vision of why science matters, e.g. in feeding the world, controlling diseases, water supply, energy production, climate change, etc. to generate a vision of pursuing a greater good for humanity. Careers advice should emphasise not just potential jobs in science, but the other career paths that open up when people study science, talking about 'careers from science' as much as 'careers in science'. Science should be seen as a vital part of a broad education, with an emphasis on how it works, not just factual recall. It needs to address the interests of girls and other marginalised groups, and make stronger links outside the classroom to demonstrate its on-going relevance. Finally, we really need to invest adequately in, and support, science teachers, or none of the above will happen.

Liz Bell

CMP *Making progress* training day

A new initiative has been developed by Coalition for Medical Progress (CMP) to train scientists to go into schools and talk to young people about the uses of animals in medical research. The hope is that this initiative will have massive positive impact on the debate about ethical animal research by increasing public understanding and, consequentially the support of this. CMP aims to make a national, coordinated network of school speakers, and aims to be able to provide a volunteer to every school that requests a speaker within 2 years. Some pharmaceutical companies, in particular Pfizer, have well established school speaker programmes but these do not cover the entire country which is what CMP aims to do. Although there has been increasing public support of animal research in recent years, CMP feels the battle is not yet won because there is still a lack of real understanding of science. This initiative will aim to reinforce the public 'acceptance' of science and educate them about it. The initiative has come at a great time as the new science curriculum for schools has an emphasis on research ethics and this provides a niche into which school speakers can fit.

I attended the first *Making progress* training day on 5 August at the Wellcome Centre in London. Personally, I wanted to increase my confidence about speaking to school children about animal research. I have no problems talking to adults about it but wanted to hear more from experienced speakers about the common problems that occur when talking to a younger audience. I was mid-thesis writing at the time and wondering how much I would learn from the course, but I was totally stupid to be apprehensive. The training day began with a speech from John Meredith (CMP) about the aims of the course and an ice-breaker. It was amazing to meet so many volunteers from diverse scientific areas and countries and to hear about each research area. What really struck me was that each person has such great passion and enthusiasm for what they do. Rob Kitson and Caroline Cutler (EdComs) talked about engaging a young audience, drawing from their own experiences in the classroom as teachers. Ian Garrod (Pfizer), who has years of school speaking experience, gave a lot of brilliant advice about the issues and difficult questions from young people. He showed the presentation he gives to schools, which gave great ideas for things to include when preparing talks. The real highlights of the day were the talks by the volunteers. Before attending the day we were asked to prepare a 5 minute talk on an animal research-related topic. All the talks were unique and it was really good to get feedback from experienced teachers and schools speakers about the good and bad bits.

Training days will be occurring across the country in the coming year. CMP would like to encourage volunteers from all scientific areas who want to share their knowledge with young people. Contact John Meredith (j.meredith@medicalprogress.org) for more details and to register for volunteer updates.

Fiona Randall

Get involved – write an article for *Physiology News*

Have you done something you'd like to recommend to other young scientists, attended an amazing training course or got an issue you'd like to get off your chest? If you enjoy writing then why not contribute to *Physiology News*. We have an annual prize of £200 for the best published article written by an Affiliate Member or an author within 2 years of obtaining a PhD.

Campaign for Science and Engineering

CaSE has been looking at ways to address the skills shortage evident in most areas of science, technology, engineering and mathematics (STEM). There are three main strands to this work: improving education, facilitating diversity and ensuring the UK is attractive and welcoming to international students and workers.

Our first report in this area, published last June, developed from a CaSE meeting at the House of Lords on *Secondary science education*, identified as the critical period for boosting numbers of science graduates. Our second report, *Delivering diversity: making science and engineering accessible for all,* followed on from an Opinion Forum meeting on *Under-represented groups in science and engineering*. Enhancing the diversity of STEM students and workers will not only increase the size of the workforce, but also its innovative potential, aside from its merit on equality grounds. Finally, we are preparing to launch a report based on our Opinion Forum meeting on *International scientists and engineers* held this July, which you will get a taste of here.

The Government has the ambition of making the UK a world leader in science and innovation. For this to happen, we need the best and brightest scientists and engineers from the UK and around the world to study and work here. As well as helping us address skills shortages, international scientists and engineers benefit the UK in many ways, such as increasing diversity and therefore innovation and in facilitating international collaborations.

It is important to be aware of various tensions around international students and workers. For instance, international workers may ease our skills shortages; this takes the pressure off making sure that our own education system can produce the graduates we need. However, retaining STEM workers here from developing countries could result in 'intellectual asset stripping'.

Hilary Leevers.

International students now play a vital role in keeping course numbers up in many of our universities, as do the international academics teaching those courses. Furthermore, the fees of international students make an important contribution to universities and their living expenses, to the wider economy. On the other hand, there are concerns that high levels of international students may impact upon how some courses are perceived or taught.

Looking at the university subject grouping of anatomy, physiology and pathology, international students make up a modest 10% of students (undergraduate and graduate combined). However, the number of overseas students is growing 10 times faster than UK students, rising 21% from 1380 in 2005 to 1670 in 2007, as compared with a 2% rise in UK students from 14945 to 15260. It is essential that rising student numbers are properly attributed so that we can understand their implications and not interpret them as indicating that schooling problems have been dealt with.

Universities will be the sector most affected by the points based visa system which is currently being rolled out. There is much to be welcomed in the new system: the ability of highly-skilled workers to be granted a visa to seek work, the flexibility of the system to respond to labour shortages and the granting of recent graduates with an opportunity to stay in the UK to seek work. However, the confusion and haste with which the new system is being introduced is raising some anxiety, as is the unresolved question about the status of academic visitors.

The UK must also be prepared for changes in the relative attractiveness of different destinations for STEM students and workers. So many factors in the international world may affect immigration flow and, indeed, emigration. Some of these are self-imposed, for example changes in the visa system. Some of these are external; for instance moves by home nations to encourage their emigrants back. And some of these factors are global and hard to predict let alone plan for, the most shocking instance of which is the current financial crisis. It is hard to know how this will eventually affect different countries as a destination of choice for work or study, but we can be sure that it will.

CaSE reports are sent to politicians and policy makers as well as our members, and lay the basis of our responses to relevant consultations and continuing campaign work.

Although we have not yet launched the international report, we have already brought our concerns to the attention of ministers and responded to a consultation on the new visa system. We urge the Government to ensure that it has a wide-ranging and coherent vision for STEM skills in the UK, incorporating the role of international workers and students.

Hilary Leevers
Campaign for Science and Engineering, London, UK

All of CaSE's reports are available at www.sciencecampaign.org.uk/documents/index.htm
The Physiological Society is a member of CaSE and we appreciate its support and active involvement. To learn more about our work, please visit www.sciencecampaign.org.uk

A maverick view of *Physiology News*

Authors of articles in *Physiology News* are encouraged to open up new fields of study and to question whether it is possible to improve the peer review of the science or non-science content of some articles.

What does one do if each and all relevant editorial boards for the last 100 years have been actively supporting peer reviews of a false scientific concept and so clothing the muscle literature with the erroneous opinions that they have become the establishment views of editorial boards – all without any explicit dissent by *Physiology News*.

Thus, the view that muscle protein was able to convert the chemical energy of adenosine triphosphate into the mechanical work of shortening has been held for a century, although based on an experimentally unsupported assumption and quite at variance with the Joule / Helmholtz concept of the First Law of Thermodynamics. This view of the First Law of the 1840s has been accepted and the SI unit of molecular energy is now the Joule.

The American physiologist Wallace O Fenn published the right ideas in 1923–24, but his work has been largely neglected by peer reviewers and editorial boards. However, after being denied printing space by the editorial boards of five reputable journals I have been able to publish an article on the unorthodox views of Joule's and Fenn's work in the open access journal *Int J Mol Sci* (2008, **9**, 1730–1752**)** ... and this is now available to anyone interested.

The unsupported view widely held by muscle scientists is well illustrated in a multi-author paper on x-ray analysis in *Science* (Rayment I *et al* [1993] **261**, 50–58). The analysis of x-ray structures is very important but the first sentence gives views, held presumably by all 10 investigators, that are totally at variance with the modern Joule / Helmholtz views of the First Law of Thermodynamics. The sentence reads: 'Motility is one of the characteristic features of many living organisms and involves the transduction of chemical into mechanical energy' (my underlining).

Physical chemists will note that this false deduction is not put as a working hypothesis but as a definite statement. The wrong views are widespread in the muscle literature and include support by the editorial boards that own the largest impact factors. Your Editorial Board is no exception, but all peer reviewers and editorial board members clearly need to give reconsideration to this field of muscle science. Mechanical work can produce heat energy, but not the reverse.

Wilfred Faraday Widdas*
University of London, UK

Editor's note:
Professor Widdas' ideas about muscle and energy are for others than me to debate. I am, though, a bit puzzled by his remarks about *Physiology News*.

Although *Physiology News* has an Editorial Board, this does not operate in the way that learned journal editorial boards do, since *Physiology News* is a magazine and not a scientific journal. Submissions to *Physiology News* are not peer-reviewed in the traditional journal sense, either by external experts or by the Editorial Board. They are *read* by the Editorial Board, and sometimes edited for clarity, but that is all.

It is hardly a secret that maverick views have a harder time getting into print in scientific journals than 'mainstream' views, and are subjected to tougher scrutiny. However, this is one of the prices for having peer review. There are now so many scientific journals that a determined author will always find an outlet, and internet-based communication of scientific ideas and data offers more ways for theories to find their audience.

Our science *News and Views* articles are mainly 'sourced' by asking authors of recent papers that caught our eye in the peer-review physiology journals if they would like to write a short perspective on their paper, and its scientific context, for a slightly more general audience. Given this, these articles in *Physiology News* necessarily reflect the kind of science published by peer-review physiology journals. One could certainly call that 'mainstream', but to me this is a long way from the conscious policy of suppression of the scientifically unorthodox that Wilfred Widdas seems to be implying.

* We are saddened to report that Wilfred Widdas died peacefully in his sleep on 29 October. An appreciation will follow in a future issue.

Hairs' apparent

I can shed some light on the photograph in your last issue (*Physiology News*, **72**, 48).

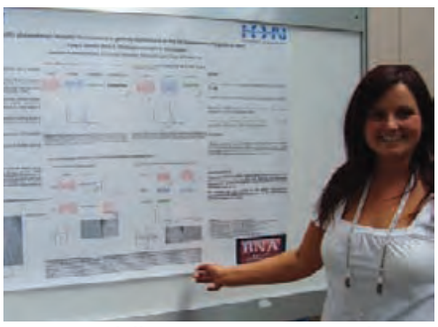
The woman on the left in the front row is Pat Barford. She graduated with a PhD in biochemistry from Cardiff University and moved to Leicester with her husband, Derek, who was a lecturer at what was then Leeds Poly. She worked on the biochemical side of Reg Chapman's work then, but shortly after that Derek moved to the medical school in Birmingham and Pat left Leicester University and took up a post at Aston University, I think. The woman on the right is Josie, who was Reg Chapman's technician. The photo is probably from 1971.

David Cotterrell
University of Chester, UK

Make the most of opportunities to travel – conference attendance as a PhD student

Attending conferences is part of the job when you are a scientist and, in my opinion, one of the best bits and great fun. Doing a PhD or even a post-doc in the lab can be isolating, working alone on a focused project. Attending a conference, if you make the most of it, can be invigorating and gives you the chance to see what other people do, how they do it differently or even how you do it better! Every aspect of a conference is a learning experience that allows you to think about your science, think about other peoples' science and think about your own future in science. As scientists at the very early stages of our career, conference attendance is the gateway to our futures, the chance to meet face to face with other scientists, see how they work and whether we'd like to work with them or in their area.

What I am really trying to do in this article is make you aware of the brilliant funding opportunities for travel available to PhD students and young post-docs. There are more travel awards available at this stage, and this reflects the invaluable



Fiona Randall presents a poster at the FENS meeting in Geneva (above); Social activity staff pictured with Naturally 7, who played at the opening night of the FENS meeting (below). Daniel Haggerty, Newcastle PhD student, takes time out from the IBRO conference in Australia (bottom).

opportunities that attending conferences provides for young scientists. Conferences provide the chance to present your work to a new audience, and discuss ideas and network, and see the world. You just need to convince your supervisors to let you out of the lab!

During my PhD I have kindly received funding to present my work from The Physiological Society, British Neuroscience Association (BNA), Federation of European Physiological Societies (FEPS), International Brain Research Organisation (IBRO), Guarantors of the Brain and the Graduate School at Newcastle University. I have presented posters and talks at a large number of conferences ranging from Harrogate to Australia. I have been able to meet top researchers in my field, people from other areas of research and other young scientists. It is great to mix with other young scientists and exchange ideas and discuss experiences. Talking about work in this setting can help you to think about where you want to go in the future, and there are worldwide opportunities. There is always a large programme of symposia where you can hear the lead scientists in your specialist area speak and also learn about the great array of work that goes on outside your field. This is a great place to put names to faces - those big names on the papers you read have a face you can remember - this is especially good if they come to chat to you at your poster! Submitting your first abstract to present at a conference is so exciting. It reminds you that your work is important and you can be proud to show it off to the scientific community. Poster presentations provide a perfect opportunity to practice talking about your work to a new audience in a fairly informal manner, where you can chat, exchange ideas, brainstorm. Giving talks can be daunting but really rewarding at the end when the audience give feedback and ideas.

Conferences occur all the time, all over the world. It is definitely worth finding out the best conferences in your field. Choose the ones with good science AND a good location. Attend the conference social programme - they always provide a more informal environment for networking!

The Physiological Society provides travel awards up to £400 for Affiliate Members to attend conferences up . See www.physoc.org for details.

Fiona Randall

Young Physiologists' Symposia

Each year, The Physiological Society provides support for small groups of scientists at the early stages of their research careers to set up and run a scientific meeting.

Organising a scientific meeting is complex and requires the development of management skills – with regards to people, time and budget – all of which are useful in the pursuit of careers in and outside of the lab.

In 2008, The Society supported two Young Physiologists' Symposia (YPS) – one in Manchester earlier in the year, and the second, reported here, which ran as a satellite to Physiology 2008. The feedback from organisers and delegates, as always, was positive: organisers value the opportunity to develop skills outside of research, and delegates appreciate the opportunity to present their work amongst their peers.

In 2009, we will be supporting four events as outlined in this section. We hope this increased support will enable a greater number of early-stage scientists to benefit from the opportunities YPS offers.

More information regarding this scheme can be found on our website at www.physoc.org/education.

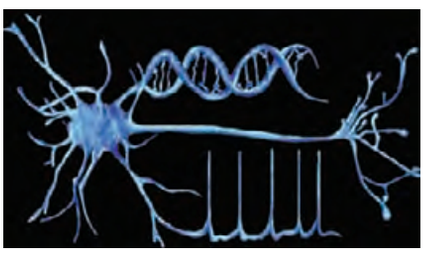
Chrissy Stokes

Experiment meets theory

Lesley Caldwell reports on the Young Physiologists' Symposium at the University of Cambridge

The 2008 Young Physiologists' Symposium, *Experiment meets theory: integrated approaches to neuroscience*, was hosted by the Department of Physiology, Development and Neuroscience (PDN), at the University of Cambridge, UK on July 12 and 13, preceding The Physiological Society's Meeting, Physiology 2008.

Young Physiologists' Symposia – 2009



Sheffield University
6–7 April
Physiological signalling: from genes to function

The symposium will provide an opportunity to showcase research on physiological signalling, with a focus on multidisciplinary approaches, such as microscopy and genetics. Sessions will include: cardiovascular physiology, metabolism and endocrinology, neuronal and sensory physiology and non-excitable cell signalling.

Registration is now open. All abstracts will be accepted for poster presentation. For more information please visit www.bms.dept.shef.ac.uk/yps or contact yps@shef.ac.uk.

University College Dublin
7 July
Muscle: function and dysfunction

The symposium will include sessions on skeletal muscle plasticity in health and disease and the role of smooth muscle.

University of Leicester
23 – 24 September
Ion channels and receptors in cell physiology

Young Physiologists' Symposium
University of Leicester

This symposium will focus on how ion channels and receptors regulate physiological processes in cardiac, neural and vascular tissues as well as in apoptosis. The presence of leading researchers in the four featured areas will provide the young investigators attending the meeting with an unprecedented opportunity to hear cutting edge research in their selected areas. Additionally, the breadth of research areas being covered across the sessions provides exposure to a broad range of cell physiology techniques.

For more information please visit www.le.ac.uk/CPP/events/events.html or contact yps@le.ac.uk.

Young Life Scientists' Symposium 2009 (YLS2009)

The Physiological Society will also be supporting YLS2009, which will be hosted at Bristol University in Spring 2009. The title of the symposium is *Neurological disorders: from molecules to medicine* and will include sessions on degenerative disease, mental health and regenerative medicine.

This event has been co-sponsored by the Biochemical Society, the Genetics Society, the British Pharmacological Society and Promega, who will be supporting *The Promega UK Young Life Scientist Competition*.

If you would like more information on YLS2009, please email YLS-09-Bristol@bristol.ac.uk.

The symposium was organised for young scientists by young scientists (neuroscience PhD students and post-docs from the University of Cambridge), providing an excellent opportunity for presenting cutting edge experimental and theoretical neuroscience among peers.

The symposium attracted over 100 delegates from 16 countries, and featured 24 oral presentations and 47 posters organised into three sessions: *Intracellular signalling in health and disease*; *Information processing in neurons and neuronal networks*; and *Neural control of homeostasis and behaviour.*

The standard of presentations was very impressive, creating an incredibly difficult task for our judges (academic volunteers from PDN). We awarded prizes for the best oral presentation (Talitha Kerrigan, *Alzheimer's disease: a result of the deterioration in K^+ channel homeostasis?)* and for the three best posters (First prize: Tomás Ryan, *NMDA receptor molecular evolution*). A prize was also awarded for the students' favourite presentation (Alexander Arenz, *Synaptic representation of whole-body motion in cerebellar granule cells*).

To enhance the, already exciting, programme, Michael Shadlen (Professor of Physiology and Biophysics, Howard Hughes Medical Institute, USA) gave a well received and inspiring key note lecture, *A neural mechanism for decision making, or how I learned to stop worrying and love the bound*.

Following the first day of talks, the organising committee hosted a symposium dinner and wine reception in the beautiful dining hall at Peterhouse College, the oldest college at the University of Cambridge. This provided an excellent opportunity for the delegates to mingle in more informal surroundings.

To support the event, additional funding was raised from the MRC, Chroma Technology Corp. USA, Cairn Research, the Company of Biologists and the *Journal of Experimental Biology*. In addition, the International Brain Research Organisation (IBRO) provided £4500 for travel grants, which enabled students as far afield as the Ukraine and India to attend the meeting.

Young Physiologists' Symposium 2008 organising committee (above): back row from left: Amanda Sferruzzi-Perri, Xavier d'Anglemont de Tassigny, Arne Nagengast; centre row: Yevheniia Mikheenko; front row: Joyce Lam, Olga Larina, Lesley Caldwell (Absent: Rebecca Rancourt and Kojiro Yano). Delegate packs (right) each included a cuddly neuron toy. Peterhouse college reception and dinner (bottom).

I would like to express my gratitude to the hard working committee and to The Physiological Society for their funding, support and advice, especially Nick Boross-Toby and Christabel Stokes. I would also like to acknowledge the invaluable help of our judges and other members of the Department, namely Alan Cattell and Aileen Briggs.

Lesley Caldwell
PhD Student, Schwiening Lab, Department of Physiology, Development and Neuroscience, University of Cambridge, on behalf of the Young Physiologists' Symposium Organising Committee.

Undergraduate Prize for Physiology 2008

Each year, The Society offers universities throughout the UK and Ireland the opportunity to nominate a student to receive an Undergraduate Prize for Physiology. Nominations, made by The Society Representative, can be for an outstanding student who has performed consistently well throughout their degree, or for a student who has completed the best BSc Honours physiology research project.

This year, nominated students were awarded a prize of £100, free Society membership for 1 year and a certificate of achievement. We are pleased to announce here the 2008 awardees.

Many additional students were also awarded 'runner-up prizes' of a year's free Society membership.

Congratulations to all students on their achievements!

Society Representatives will be notified by email once the nomination process begins for 2009. Enquiries relating to the prize should be directed to Irrum Magre (imagre@physoc.org / 0207 269 5726).

Irrum Magre

Undergraduate Prize winners 2008

Ruth Mears	Cardiff University
Ales Towers (prize shared with Sarah Towner)	Keele University
Sarah Towner (prize shared with Alex Towers)	Keele University
Umair Shafique	King's College London
Laura Staniland	Manchester Metropolitan University
Orla McDonnell	Queen's University Belfast
Luke Mappley	Royal Holloway, University of London
Benjamin William Sansom	St George's, University of London
Ciara Lee	University College Dublin
Farhabanu Manga	University College London
Luisa Mowat	University of Aberdeen
Simon Anderson	University of Birmingham
Daniel Towie	University of Bristol
Arjun Chandna	University of Cambridge
Laura Brown	University of Dundee
Jennifer Bush	University of Edinburgh
David Paton	University of Glasgow
Tavga Muhammed	University of Huddersfield
Sarah Bailey	University of Leeds
Yusuf Bhagatte	University of Leicester
Rebecca Morse	University of Liverpool
Hayley Dingsdale	University of Manchester
Nichola Jane Conlon	University of Newcastle upon Tyne
Louise Gates	University of Nottingham
Alice K England	University of Sheffield
Jacqueline King	University of Southampton
Katy Elizabeth Robinson	University of St Andrews
Shona Cowper	University of Strathclyde
Lisa Kennedy	University of Sunderland
Claire H McTaggart	University of Warwick
Helen Webb	University of Wolverhampton
Hayley Tyrer	University of York

Life Science Careers Conference 2008

Wednesday 26 November 2008 (13:00–18:00)
New Hunt's House, King's College London, Guy's Campus

The Biosciences Federation is holding a custom-made careers conference designed by scientists for scientists. The conference will highlight some of the opportunities available to life science graduates, specifically targeting students who are looking for ideas and contacts related to careers in the biosciences.

The conference, sponsored by Astra Zeneca (with additional support from the Biosciences Federation, The Physiological Society, the Biochemical Society, the Society for Endocrinology and the Society for Experimental Biology), will feature talks from bioscientists who are working in different careers ranging from research to science communication.

In addition, there is a lengthy session on presenting yourself in a CV (with specific examples of bioscience CVs), as well as the opportunity to visit the exhibition, which includes employers and not-for-profit organisations.

Full programme and online registration (£10, including refreshments) at www.physoc.org/lscc2008.

Registration on the day if space permits.

100 years ago

The effects of low atmospheric pressures on respiration. AE Boycott & JS Haldane (1908). *J Physiol* **37**, 355–377.
Alveolar air on monte rosa. R Ogier Ward (1908). *J Physiol* **37**, 378–389.
The effects of want of oxygen on respiration. JS Haldane & EP Poulton (1908). *J Physiol* **37**, 390–407.

This time I want to draw attention to three papers that appear together in the December 1908 issue of *The Journal of Physiology*. The key linking figure in these papers, and a co-author of two of them, is James Scott Haldane CH FRS (1860–1936). Haldane was the leading respiratory physiologist of his day, though outside physiology he is probably less famous than both of his children. These were John Burdon Sanderson ('JBS') Haldane (1892–1964), the mathematician turned evolutionary biologist and writer, and the novelist and poet Naomi Mitchison (1897–1999).

JS Haldane first seems to have become interested in respiratory physiology via his work on mine safety and the role of gases. As was typical of the day, self-experimentation was the norm for Haldane's work. In a famous study a few years earlier (Haldane & Priestley, 1905), Haldane and John Priestley (1880–1941) had established that blood CO_2 levels were the key regulator of ventilation. To do this they collected samples of their own alveolar air for the measurement of O_2 and CO_2 – used as a surrogate for measuring blood gas levels – under different atmospheric pressure conditions, or more specifically: '... at the bottom of Dolcoath Mine in Cornwall (2240 feet below sea-level); at the top of Ben Nevis (4406 feet above sea-level); and in the chamber for treating patients with compressed air at the Brompton Hospital, London (at an excess of pressure of about two-thirds of an atmosphere).'

The three 1908 papers share the habit of the authors being simultaneously the experimental subjects. The experiments in the first paper were carried out: '... in the large steel [pressure] chamber recently presented to the Lister Institute by Dr Ludwig Mond. This chamber... is sufficiently roomy to enable three persons to work comfortably ... Any desired negative pressure can easily be obtained.'

In this paper, Boycott and Haldane extend the earlier analysis of Haldane and Priestley to lower pressures, and hence lower levels of ambient and alveolar O_2 than had previously been possible. Their main conclusion is that CO_2 levels remain the key respiratory controller until pO_2 falls below about 60 mm Hg, at which point what we would now call 'hypoxic drive' (a direct stimulatory effect of the reduced pO_2 on breathing) becomes apparent. They also note: 'When the alveolar [pO_2] falls to about 30 mm [Hg], urgent symptoms (marked cyanosis and tendency to fainting) are produced.'

In the third paper Haldane and Poulton validate and extend the conclusions of the Boycott and Haldane paper using different gas mixtures at normal atmospheric pressures. This paper employs a re-breathing set-up (illustrated in their Fig. 1) that will look familiar to anyone who has ever been involved in undergraduate physiology classroom respiration experiments with Douglas bags or drum spirometers. Haldane and Poulton actually mention classes, in another excerpt that will ring bells with some readers: 'Complete loss of consciousness without any noticeable signs of preceding hyperpnoea has also been observed by one of us in a student of physiology who was performing the class experiment of re-breathing the air of a bag through soda-lime, so as to demonstrate the effects of gradually increasing want of oxygen apart from those of a simultaneous increase in the [%] CO_2. He showed the usual marked cyanosis, but did not even notice any discomfort or show any signs of hyperpnoea.'

This demonstration of hypoxia remains a common practical class experiment, though usually without inducing the experimental subject to lose consciousness – at least in the modern era. The experimenters of 1908 were made of stern stuff, though, even the then 48 year old Haldane. At the end of one experiment (reaching an alveolar pO_2 of around 25 mm Hg) he is recorded as: 'At end very blue and confused. Great hyperpnoea and distress, much twitching.'

The middle paper of the three, by R Ogier Ward, takes a quite different form. Ward was also an experimental subject in the experiments in the Boycott and Haldane paper. We learn in his own paper that he was 'nominated by the Royal Society to the International Laboratory on Monte Rosa.' This laboratory (still in operation) was a mountain hut dedicated by Queen Margherita of Italy in 1893 as an altitude science research station. It stood at 15 000 ft near the peak of Monte Rosa, the second highest in the Alps. Ward states: 'The object of these experiments was to compare the effects upon the composition of alveolar air, produced by living at great altitudes, with such variations as are obtained by artificially altering the barometric pressure ...'

Ward's paper is a curious mix of travelogue and experimental account, reminiscent of a personal journal and conjuring up an era of intrepid travellers. At points I was reminded of Eric Newby's famous *A Short Walk in the Hindu Kush* nearly half a century later. Ward writes: 'On August 3rd, the day of arrival, [I] experienced in a slight degree symptoms, such as shortness of breath, headache, chilliness, which may be attributed to the effect of altitude; these however passed off, but were succeeded on the following day by a severe bilious attack which came on during the night and lasted twenty-four hours.'

Although Ward, like Haldane back in Oxford, was suffering for science, one of his traveling and experimental companions, 'WDH', had far worse mountain sickness, despite being 'undoubtedly the better physically trained.' Manfully, they completed their readings despite the discomforting symptoms.

Part of WDH's misfortune, it appears, was to have a lower 'normal' alveolar pO_2 than Ward. Indeed, one of the interesting things that emerges from these experiments on a few select subjects is the pronounced variability between individuals of parameters like the alveolar CO_2 'set-point' for respiration.

Among the authors, Arthur E Boycott (1877–1938) was one of the founders of experimental pathology in the UK, later becoming Professor of Pathology at University College London, and elected FRS in 1914.

Haldane published many papers with students or other junior members of the Oxford Physiology Department. Poulton and Ogier Ward are listed on the 1908 papers as 'B.A.' and thus seem likely to have been clinical medical students who had earlier completed physiology intercalating degrees. Both subsequently went on to distinguished medical careers, Poulton as a consultant physician at Guy's Hospital, and Ogier Ward as a leading urological surgeon. A nice account of Haldane's science, including his famous work on decompression sickness and its avoidance in divers, can be found in West (2008).

Austin Elliott

Haldane JS, Priestley JG (1905). *J Physiol* **32**, 225–266.

West JB (2008). In Poulin MJ & Wilson RJA (eds) *Integration in Respiratory Control.* Springer.

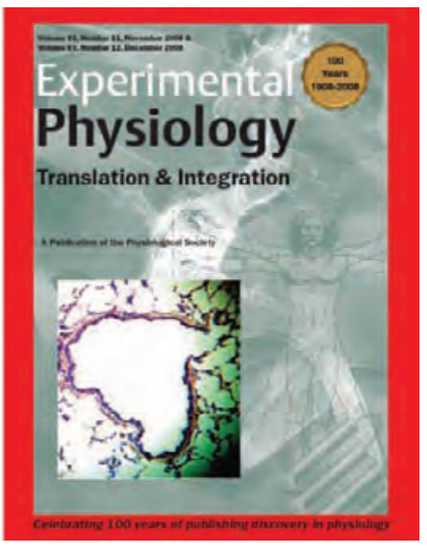
Experimental Physiology
Translation and Integration

Celebrating 100 Years of Publishing Discovery in Physiology 1908-2008

Editor-in-Chief David Paterson hosted the *Experimental Physiology* Editorial Board Meeting and a splendid Centenary Dinner at Merton College Oxford (*above*) on 12 September. Editors attending the meeting (*below*) included (*from the left*): Denis Noble, Peying Fong, Nick Simmons, Mike Shattock, Mike Hogan, John Coote, Mike White, Jim Deuchars, Stuart Egginton, David Paterson, Nic Smith, Kenneth Baldwin, Clive Coen, Margaret Brown, Paul McLoughlin, Peter Raven and Steve Harridge.

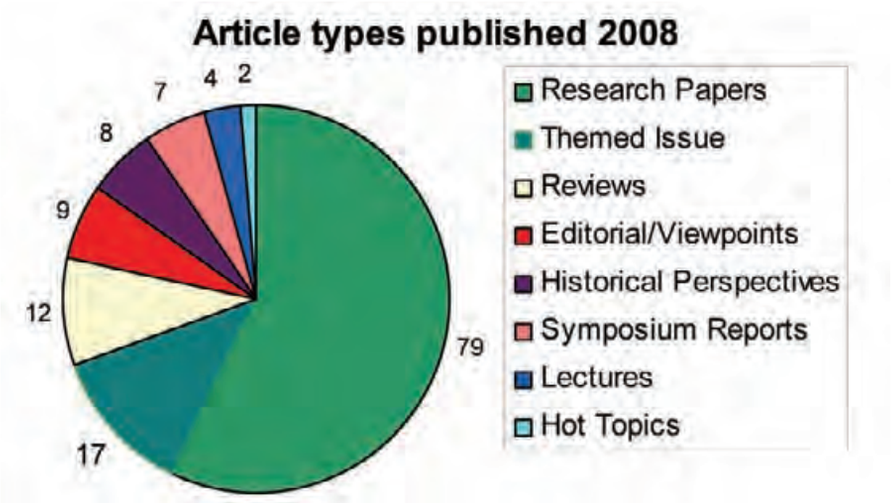
Historical Perspectives

The final Historical Perspective article has now been published. The full series is available online as an Article Collection or 'Virtual Issue' (http://ep.physoc.org [Article / Subject Collections]).



The size of the journal will be increased from 1000 to 1200 pages in 2009. Submissions have continued to increase since publication of the journal moved to Wiley-Blackwell in 2004 with an allocation of 1000 pages and, despite reducing the acceptance rate, there are more acceptable papers than pages available for publication.

The 12 monthly online issues of 2008 have contained an interesting mix of articles with more invited articles than usual to reflect the centenary year (see pi chart, right) .



The Journal of Physiology

Symposia

Friday 20 March 2009
Altered placental functions as a cause of altered fetal growth
At Society for Gynaecological Investigation, Glasgow, UK.

Monday 20 April 2009
The world within – impact of the intestinal microbiota on whole body physiology and pathophysiology
At Experimental Biology 2009, New Orleans, LA, USA.

Wednesday 8 July 2009
Novel insights into oestrogen actions
At The Physiological Society Annual Meeting, Dublin, Republic of Ireland.

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

For full details of these, and other Symposia as they are approved, visit http://jp.physoc.org/misc/sympspecial.shtml

Developments in open access publishing

Springer buys BioMed Central. Is open access publishing becoming mainstream?

Early in October, BioMed Central (BMC), the first free-to-read journals publishing company, was sold to the large commercial publisher, Springer. BMC was set up in 2000 as statement of faith by proponents in open access publishing, with authors and sponsors paying the costs of publication. To date BMC has relied heavily on sponsorship to cover costs, and the inequities of author-pays publishing – only the well-funded can pay – are still being debated. It remains to be seen whether current full open access to all articles in BMC journals continues, but the acquisition is a sign that the open access publishing model is coming of age. According to the US Library Journal, this development 'is a significant event in the history of open access publishing ..., as a leading commercial publisher has now expressed confidence in a business model once deemed, at best, experimental, and often called untenable.' In the same month the Open Access Scholarly Publishers' Association (http://www.oaspa.org/) was launched by 10 founding member organisations involved in open access publishing, to support and represents the interests of open access publishers.

Open access and citations. The first randomised trial shows no effect

Another thread in the open access movement relates access to articles with usefulness – are open access articles cited more? If access to relevant articles is a problem for scientists, they should be. A number of studies have been published, with conflicting results, but in July the *British Medical Journal* published the first truly randomised controlled trial of open access. The study by a group from Cornell University used articles from the American Physiological Society journals, making random articles open access and then measuring citations after a year. No effect of open access was found, suggesting that while patient groups may be troubled by lack of immediate access to the latest research, researchers are not. It has been pointed out that a year is very early in the life of a physiological research article to be measuring its usefulness and lead author Phil Davis has indicated that the study will continue.

NIH consultation. No change in policy

The NIH has completed a consultation with publishers, patient advocates, scientists and university administrators on its policy requiring funded investigators to submit their final accepted manuscript to PubMed Central within 12 months of publication. They report broad support for the policy and a jump from 19% compliance during the period of voluntary submission (2005–7) to 56% compliance following the introduction of the new policy mandating submission. The report states that the policy 'is designed to preserve the critical role of journals and publishers in peer review, editing and scientific quality control processes'. NIH will continue to consult with community to implement the policy in 'the most efficient and effective manner possible'.

Carol Huxley

References

LJ Academic Newswire Oct 7, 2008 (http://www.libraryjournal.com)

Davis P. M. et al. (2008). Open access publishing, article downloads and citations: randomised controlled trial. *BMJ* **337**, a568.

http://publicaccess.nih.gov

The disinherited hyphen

Experimental Physiology, like *The Journal of Physiology,* has a well-deserved reputation for its consistent style. The consistency owes much to the *Black Book*, the style guide compiled in The Society's Publications Office over the years and updated as conventions change. Biochemical nomenclature has normally accorded with that in the *Biochemical Journal.*

In 1992 PC Pook *et al*. submitted a Rapid Communication to *Experimental Physiology*. It was quickly accepted (**77**, 529–532) and the copy-edited proof sent to Jeff Watkins, the corresponding author. Jeff asked why 2 mM Mg^{2+} had been changed to 2 mM-Mg^{2+}. On being told that the *Biochemical Journal* used a hyphen, he again said 'Why?' When questioned, the longest-serving member of the *Biochem J* editorial staff said 'Because that's how it always has been.' Although The Physiological Society likes to maintain its own traditions, it had no compunction about casting off those of the biochemists. The hyphen was ejected from both our journals as rapidly as their Press deadlines allowed. Interestingly, it disappeared from the *Biochemical Journal* in January 1993.

Ann Silver

The history of physiology

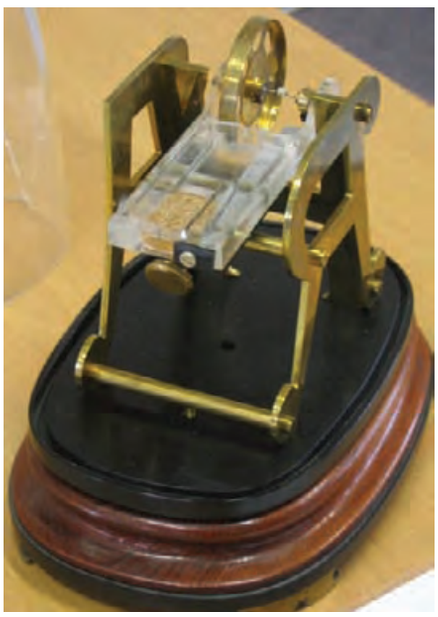
The Society's History & Archives Committee actively promotes interest in the history of physiology. We aim to preserve the experiences, skills, ingenuity, anecdotes and artefacts of physiology. The Committee is seeking help from Society Members in two of its activities – preserving physiological equipment and recording oral histories.

Physiological equipment

The Committee would very much like institutions and departments to identify and maintain any historically important physiological equipment. In particular we look out for unique pieces of equipment, usually hand-made or modified in departmental workshops, which have contributed to the advancement of the subject. If you or your colleagues (including older technicians) are aware of any such equipment please do let us know. We cannot promise to take them off your hands – a lot depends on size – but we can either ask the Science Museum to store particularly important articles or suggest museums local to you who are often delighted to exhibit them.

Oral histories

The Committee oversees a growing collection of oral histories from



Historically important physiological equipment on display at The Society's Cambridge meeting – Richard Adrian's 'muscle bicycle'(above) and the Keith Lucas spring pendulum, 1908 (below).

people who have been involved in physiology. The individuals include technicians, research assistants as well as physiologists. Indeed the former often give more insights into what really happened than the latter! The histories are recorded discussions which are transcribed and stored in The Society's archives. What interests us, and we hope future historians of science, is how things happened; what the circumstances were which lead to a particular piece of work or discovery; what the cultural context of the time was. If you can suggest anyone whose experiences you think are worth recording, we would be delighted to hear from you.

If you are able to help in either activity, please do get in touch with me (dwalters@sgul.ac.uk)

Dafydd Walters
Chair, History & Archives Committee

Memorable technicians

Physiology News **67** (p. 47) contained a memoir of Jock Austin that I wrote with Iain Donaldson. Two other technicians in the Edinburgh Physiology Department in the 1950s stick in my mind: Pat Smith and George Renwick. As a student, I had little contact with the Head Technician Tom May.

Pat worked in Surgeons Hall (the home of the Royal College of Surgeons of Edinburgh) as well as in the Department of Physiology. As befitted an Irishman, he was keen on the horses and ever ready to place bets for any one who asked. His stories from his early years in the department were usually gruesome. Edinburgh at that time had a considerable population of meths drinkers (methylated spirits produces prolonged drunkenness associated with optic neuritis and blindness). These unfortunates used to congregate under the back windows of the department from which the lab boys would drop meths-soaked cotton wool pledgets. They also dropped penny coins – but here's the rub – the horrid boys first made these red hot in a Bunsen burner.

George was much younger than Pat – a lab boy rather than a technician. He was always cheerful despite marked kyphosis (TB was then rife in Scotland with all students having a compulsory annual chest X-ray). When one of Mary Pickford's visiting colleagues told George that Mary wanted some of his blood he, ever willing, gave it unquestioningly though, when asked, he did say that he'd never given any before. Luckily, Mary discovered the confusion of George, the boy, with George, one of her experimental dogs, before her experiment was wrecked.

A little bit of freelance photography one lunch time got George into hot or, rather, cold water. He had left his prints to rinse under a running tap. When the plughole blocked, the water that flowed down the stairs bore with it the identity of the perpetrator in the form of several self-portraits.

Ann Silver
University of Cambridge, UK

The Society worldwide

In 2007, David Eisner finished his term as International Secretary. David's tenure was hugely successful, and a great deal of work had been done to advance physiology as a discipline – and to advance The Physiological Society's reputation – worldwide.

However, many of the schemes we had in place were devised a number of years ago, and in response to the collapse of the Soviet Union. Therefore, this was judged a good time to review The Society's international activities. Stepping back and looking at why a society such as ours needs an international policy reveals two overarching principles:

International relations

- maintaining established relationships with outside groups and societies;
- setting up links with groups or societies with whom we have formerly had little contact.

Development

- helping to develop resources and good practice in areas where physiology teaching and/or research suffer from lack of resources.

An international strategy based on these principles would enhance The Society's profile and reputation, and support physiology internationally – which is part of our charitable objectives.

Fireside singalong at the 2006 Kiev International Workshop (above); participants at the 2006 Venezuela International Workshop (below).

Maintaining established relationships with outside groups and societies

The Society is an integral member of both the Federation of European Physiological Societies (FEPS) and the International Union of Physiological Sciences (IUPS). Key to the success of both these international bodies is the maintenance of good links between their largest members. Closer ties with other large physiological societies (e.g. American, Scandinavian, and German societies) would allow better coordination of strategy within both FEPS and IUPS.

Small activities, run in partnership with these societies, would be a good way of maintaining more regular contact than the 4 year IUPS cycle and sporadic FEPS meetings.

Furthermore, once we have established relationships with groups or societies with whom we have formerly had little contact (e.g. recently the Brazilian and Chinese societies) we need to make sure these links are preserved for longer than the initial meeting. Again smaller activities, run in partnership with these societies, would be a way of maintaining these links.

Setting up links with groups or societies with whom we have formerly had little contact

The establishment of relationships may overlap somewhat with the developmental aspects of our activities. The aim should be that The Society has contacts with those involved in physiology everywhere in the world. As mentioned above, newly established relationships need to be followed up and maintained.

Spreading resources and good practice

The development aspects of The Society's international policy are

well established. There are two ways a large society such as ours can offer help to those whose physiology is less developed:

- by providing financial support;
- by exporting the knowledge and experience of our Members.

We are lucky in this country in having physiologists of the highest standard – in both teaching and research - who have access to the very best equipment. Utilising this huge resource would not only do more for the advancement of physiology worldwide, it would save The Society money, and get more of the membership engaged in Society activities.

If we agree that utilising the knowledge and experience of our Members is the best way to help physiology internationally, then there are two ways of doing this:

- we support our Members going abroad to the places they are needed;
- we support overseas physiologists visiting the UK.

Both can be of use, however a skew towards the latter seems the more sensible, as we have state-of-the-art equipment and institutions in the UK from which foreign visitors would benefit hugely.

With these guiding principles in mind, I have been working with the Executive, Meetings, and Education Committees to review our current schemes – and draw up some new ones – in order to refresh our international strategy.

Participants at the 2006 Joint International Meeting in Brazil (above); entertainment at the 2006 Kiev International Workshop (below).

As before, International Workshops and Joint International Meetings (such as next year's meeting with the Society of General Physiologists in Woods Hole, USA) can be used to establish and maintain relationships. The same is true of the International Guests (previously Foreign Guests) scheme, which will see leading physiologists from the international scientific community attend Physiology – our Main Meeting – which in 2009 will take place in Dublin.

Maintenance of relationships is an extremely important element of this new strategy, in the past we have had an informal agreement with the American Physiological Society (APS) whereby we sponsor symposia at each other's Main Meetings. This activity – the Joint International Exchange Symposia scheme – is to be formalised and extended to include the German and Scandinavian physiological societies. Indeed the former has kindly submitted a proposal for Physiology 2009, which has been accepted alongside one from the APS. The Scandinavian society has agreed to submit a proposal for 2010 in Manchester.

As ever, The Society will work very hard in a developmental capacity, spreading resources and good practice to groups or societies where physiology needs support. The International Senior and Junior Research Grants will support physiological research overseas, through financial support and interaction with a sponsoring Member of The Society. Alongside this, the David Jordan International Teaching Fellowship will give teachers/learning support staff based within UK and RoI, or overseas, an opportunity to visit an institution of their choice in order to develop or acquire teaching methods of benefit to the teaching of physiology in their home institution.

The details for all these schemes are still being finalised, with a view to accepting applications from next year.

As international strategy touches on all the activities which The Society undertakes, Mike Spyer as Deputy President of The Society will be responsible for overseeing the strategy and its implementation.

We are always grateful to hear from Members of The Society who have contacts overseas. At the moment, we are particularly looking to expand our contacts in India and south Asia. I would very much like to hear from anyone who has knowledge of, or contacts in, either of these areas.

David G Bennett
International Activities Coordinator
dbennett@physoc.org

BIOSCIENCES FEDERATION

Learned societies and publishing

The Biosciences Federation (BSF) published a report in July with the results of several questionnaires it had conducted earlier this year. Thanks to all those who took part. The survey and report were carried out by the BSF Journals Committee, chaired by Sue Thorn of the Society for Endocrinology*. Some key details are included below as a taster.

You get more out of your society financially than you put in

You probably knew that already, but we can now show that the UK university system as a whole gets more money from bioscience societies than it spends with those societies in journal subscriptions. The survey showed that, for the 23 societies who responded, they put 2.16 times as much money into the UK university system by way of grants, meeting support and other educational services than they take out by way of journal subscription and licence fees. The societies analysed contributed almost £4M of such support in the last year. You might want to make sure your Vice-Chancellor is aware of that in the light of some of the more radical Open Access people who want only a free repository system which would probably cause the collapse of most journals and of the support that their owner societies provide.

In addition, the report shows that all the societies provide free access to much of their journal material, usually after 12 months, although many also make selected material available earlier than that, eg review articles.

Most of the societies allow researchers to self-archive free in an institutional or other repository (e.g. PubMed Central) after a delay. Most of them would allow immediate self-archiving on payment of a fee. Many of the publishers would carry out the deposit for the author, especially where a fee is paid.

Do you really know what open access is?

The survey of researchers, which had 1349 usable responses, showed substantial confusion about what open Access (OA) means. Many respondents seemed unable to tell the difference between online journals that are free at the point of use (because the library has paid a subscription fee) and Open Access ones, where all the material is free. Almost half the OA journals respondents said they read, and a third of those they published in, were not OA journals at all.

Only around 15% of the respondents had tried to access OA publication funds from their institutions or research funders to pay for author-side charges. Of these 53% had found it very difficult or fairly difficult. Sue Thorn and Steve Byford are taking part in a Universities UK working group to try to resolve this issue.

Interestingly, as regards self-archived material (usually an earlier version, such as the author's submitted manuscript), only 3.5% of respondents said they access this version if they have access to the final published version, and 67% rarely or never access the self-archived version even if they don't have access to the published version.

*The full report can be seen at http://www.bsf.ac.uk/journals/BSF_survey_report_July_2008_FINAL.pdf.

Creation of a new organisation for the biosciences

The Councils of the Biosciences Federation (BSF) and Institute of Biology (IoB) have proposed that a new organisation for the biosciences (NO) should be created. This organisation will embrace the activities and strengths of both the BSF and IoB, and add new activities that will benefit UK biosciences and provide value to the membership. A prospectus for the NO has been prepared by Richard Dyer for the BSF outlining the background to the discussions between the BSF and IoB, a reduced version of which follows. The full version, which contains more information on the finance, structures and immediate goals of the NO, is available from the BSF website (http://www.bsf.ac.uk),

The opportunity

The excitement of modern biology is palpable to all on a daily basis. Uniquely important issues are frequently discussed by the media and the public. How many in this country are not aware of the debates about stem cells, loss of species through global warming and modern agriculture, the teaching of biology in schools or what our diet is doing to our bodies? But how do the biologists join these debates about biology? If they do at all, it is through a myriad of possible routes and representing too many organisations. The need for a unified voice for all the biosciences has never been greater. Our vision is to provide that unified voice in debates about the development of policy and best practice in education, career development, legislation and the funding of research. In undertaking these roles, strong outreach to all the regions of the UK will provide strong local foci of relevant interest for all the membership including teachers, research scientists and regional organisations.

Background

The exciting diversity of the biosciences has led to the formation of very many special interest groups where scientists and others with shared interests and mission productively work together. There are, for example, scores of learned societies and medical research charities, as well as many individuals with a passion for biology, whether it is on a professional or personal basis. Although it is difficult to be precise about figures, these organisations alone probably comprise more than 200 separate and independent

organisations, while there may be tens of thousands more individuals, some with no affiliation. This landscape is unique for the biosciences: physics, chemistry, mathematics and engineering are represented by very few organisations, which are wealthy and influential.

Whilst special interest groups undoubtedly bring advantages of focus to research or fundraising, the fragmentation of the biosciences leads to huge disadvantage in other areas – for example, in outreach to schools or in representing biology to Governments and funders. In order to ameliorate this problem various groupings have come together under an umbrella organisation where matters of common interest can be dealt with more effectively than by a multiplicity of individual actions. But in the biosciences this increased effectiveness is diluted because there are several umbrella organisations (e.g. the Institute of Biology and Biosciences Federation) and some of the problems associated with fragmentation remain.

Recently the councils of the IoB and BSF proposed that a new organisation should be created that will embrace the activities and strengths of both BSF and IoB, and add new activities that will benefit UK biosciences and provide greater value to the membership. This proposal was unanimously endorsed by a joint meeting of the IoB and BSF at the Royal Society in May 2008.

Implementation group

In order to move this ambitious plan forward, the BSF and IoB have established a joint Implementation Group (IG) chaired by Sir Brian Heap. Other members of the IG are Bridget Ogilvie, Nancy Rothwell, Malcolm Press, Keith Gull, David Coates, Alan Johnston, Alan Malcolm and Richard Dyer. Members of the IG are unanimously agreed on the key issues highlighted in the box.

Currently the IG is preparing the papers that will need to be put to the memberships of BSF and IoB for the approvals necessary for these proposals to be implemented.

Key implementation issues

- Membership of NO will be open to both individuals and organisations from any sector of the biological sciences;
- The Council of the NO shall comprise a Chair and 12 members – four elected by the individual membership, four from the institutional membership and four nominated by Council to ensure that there is a good balance of representation and that the Council is fit for the purposes expected of a charity in the 21st century;
- The NO shall have a Royal Charter and continue to offer chartered status and fellowship to individual members.

Finance and structures

The NO can be launched successfully with the present combined incomes of the BSF and IoB. In 2007 the corporate subscription income for BSF was £235k and the membership income for IoB was £860k. For 2009 the total subscription income for the two organisations will be circa £1200k. In addition, the IoB raises about £200k from other sources and the BSF about £100k per annum from member organisations for identified projects. This *à la carte* funding is an important element for future development.

A full business plan for NO will be produced by mid November 2008.

The IG is not focused on the detail of the structures that may be set up within NO: that will be a responsibility of the first Council and new Chief Executive. However, the IG is determined to suggest some overarching principles for the organisation of NO and in particular that it is a flat structure with the ability to make rapid decisions.

Immediate goals for NO

Membership

There will be an immediate drive to increase the number of individual and institutional members. Currently some large areas of the biosciences are poorly represented in both the BSF and IoB.

The NO will retain a Royal Charter and offer chartered status to its individual members. An immediate goal will be to strengthen the standing of this qualification by introducing a structured "Career and Professional Development" programme. The aim will be to increase the esteem of all qualifications, including Fellowship.

Outreach

Structured outreach to schools and the public more generally will be built through the regional groups that already exist in the IoB. There is considerable scope for exciting new ventures.

The NO will also focus on increasing outreach to the membership as a whole through regional scientific meetings and high quality lectures and debates. The leadership, both executive and non-executive, will ensure that the activities of NO are not solely based in London or SE England.

Finally there is the prospect of substantially increasing the effectiveness of outreach through the media – both directly and by partnering with the Science Media Centre.

Policy work

Both BSF and IoB have been largely reactive to policy initiatives coming from governments and funders. Although these responses are important it is equally important to be proactive in order to set the national agenda. In this context national means UK as a whole and the four countries of the union.

Why now?

Both IoB and BSF could do many of the activities that are proposed for NO. But in undertaking these activities IoB and BSF would not engage all the heartlands of the biosciences. To meet the challenges of today, biology needs a single voice. Our subject needs an organisation like the Royal Society of Chemistry or the Institute of Physics which has the respect of the community as a whole and where individuals are proud to be members because of the standards maintained and the quality of project delivery. With your support NO can achieve this status rapidly: this is urgently needed and the current opportunity must be embraced.

Richard Dyer

J Murdoch Ritchie

1925–2008

J Murdoch Ritchie, Higgins Professor Emeritus of Pharmacology at Yale University School of Medicine, died peacefully on 9 July 2008 in Hamden, Connecticut, after a long battle with Alzheimer's disease. Murdoch made several major contributions to our understanding of the conduction of impulses in peripheral nerve, and was a major figure in the burgeoning field of neuropharmacology in the second half of the twentieth century.

Murdoch Ritchie (*centre*) with Larry Cohen (*left*) and Richard Keynes (*photo by Roger Thomas*).

Born in Aberdeen, Scotland on 10 June 1925, he obtained a BSc in mathematics & physics from Aberdeen University in 1944. He then took a position as a research physicist at the Telecommunications Research Establishment at Malvern in the south of England, where he was part of A V Hill's team that was instrumental in the development of radar. In 1946 Murdoch followed Hill to University College London (UCL), where Hill formed the world's first Department of Biophysics. Working with Hill as a research student on the dynamics of skeletal muscle contraction, Murdoch received a BSc in physiology in 1949. After a 2 year stint as a junior lecturer at UCL, in 1951 Murdoch moved to the National Institute for Medical Research at Mill Hill. The same year he married Brenda Bigland, herself a rising young physiologist. Murdoch received a PhD in biophysics in 1952 (for work on the production of initial heat in muscle fibres) and was awarded a DSc in biophysics in 1960, both from UCL.

At Mill Hill, Murdoch became close friends with his fellow Scot, Bill Douglas, and in 1955 they began work on the control of blood pressure by unmyelinated nerves. That same year, a young American postdoc named Paul Greengard came to Mill Hill to work and the three became friends. The following year Douglas accepted a position in Al Gilman's new Department of Pharmacology at Albert Einstein College of Medicine in the Bronx. Douglas casually suggested that Murdoch and Brenda take a sabbatical leave and accompany him, which they did. After returning to England for a year, Murdoch accepted an Associate Professorship in Gilman's department in 1958. At Einstein, Murdoch and Douglas continued their work on nerve, work that resulted in a series of classic papers in the late 1950s. Greengard also joined the department at Einstein, and the three papers on local anaesthetics that he and Murdoch co-authored in the early 1960s remain relevant today. In 1968 Murdoch was recruited to Yale as Chair of Pharmacology, bringing with him both Douglas and Greengard.

Initially with Richard Keynes, and later with Humphrey Rang, David Colquhoun and Gary Strichartz, Murdoch was among the first to apply radioligand binding to studies of the nervous system, using radiolabelled tetrodotoxin and saxitoxin to count sodium channels in peripheral nerve. He also worked (with Vic Howarth and Keynes) for several years on the production of heat in nerve and was proud to say that he closed this field, ultimately showing that it had little to do with the mechanistic basis of conduction. In addition, Murdoch made important contributions to our understanding of metabolic changes during nerve activity and the role of the Na/K-ATPase in maintaining transmembrane ion gradients. In the 1970s and 1980s, Murdoch turned to models of demyelinating disease to characterize the changes in ion channel density and conduction that accompany demyelination in diseases like multiple sclerosis. He also quantified the unequal distribution of sodium and potassium channels in myelinated nerve that underlies normal saltatory conduction. Together with Peter Gray, Stuart Bevan, Peter Shrager and Bill Chiu he was the first to show that satellite cells in both the peripheral and central nervous system (Schwann cells and astrocytes) expressed voltage-gated ion channels.

Murdoch was elected a Fellow of the Royal Society in 1976 and a Fellow of the Institute of Physics (London) in 1997. Though he had a keen, quantitative intellect and was comfortable with complicated theory, his scientific approach was strongly grounded in experimentation. One morning when I worked with him he suggested an experiment and I started going on about possible outcomes. Murdoch soon began to alternately tap both feet, a clear sign that his patience was wearing thin. He let me go on a couple more minutes and then broke in with '*Look, we can sit here and talk about it all morning or we can go and do it*'. I have retold this story countless times over the years to my own students and post-docs when they started indulging in virtual science. Murdoch simply loved the hands-on aspects of experiments, and for that reason he rarely worked with more than two people at a given time. Murdoch was in his 60s when I was in the lab, but it was still a continual challenge to match his energy. He was an early riser, and most days when I arrived Murdoch would be racing around finishing an experiment he had begun that

morning. He would then pitch in and help me. No aspect of an experiment was too tedious or trivial for Murdoch, and while I pulled patch pipettes he would scurry around making solutions or whatever else needed doing. Despite his other responsibilities, he almost never missed the patch-clamp recording in the afternoon, which typically began with him announcing '*time to get down to the verbs*'. I don't usually like someone watching over my shoulder, but I looked forward to these afternoons, since he would pepper his scientific comments with ribald innuendos involving actresses and bishops and humorous anecdotes about the giants of neurophysiology and neuropharmacology. There was never a dull day when Murdoch was around. One of the stories I like best about Murdoch is from the time he worked on the garfish olfactory nerve. When the live garfish arrived from Florida, Murdoch would prepare for the messy dissection not by donning a lab coat, but by stripping to the waist. Murdoch continued to conduct his own experiments until he closed his laboratory in 2000 at the age of 75.

Murdoch's obvious zest for life was equally evident in his personal demeanor. A charismatic figure, his bearing and lively personality naturally commanded attention. He was an avid skier, and he religiously attended Winter Brain Conferences and vacationed with his family in his beloved Zermatt for decades. In the summer, he could often be found at his home in central Vermont, much of which he built with his own hands.

Murdoch viewed sharing knowledge as an important part of scientific life. The five editions of Goodman & Gilman spanning 1965–1985 contain chapters carrying his name on the pharmacology of local anesthetics, aliphatic alcohols, and caffeine. He enjoyed writing, and he authored and edited over 70 reviews, chapters, books, and monographs. Murdoch directed the pharmacology course for second year medical students at Yale for 30 years, lecturing himself

Ritchie's lab, circa 1971.

throughout and attending most of those given by others. His legendary lecture on alcohol began with him breaking a raw egg into a glass of single malt whisky, which he then set aside. At the end of the lecture, Murdoch would raise the glass, point out that the whiskey had denatured the protein in the egg white, and then quickly down the contents in a single gulp, all to the great amusement of the students. He served on many university committees and was Director of the Division of Biological Sciences at Yale from 1975–1978. In the late 1970s, he championed the establishment of the first core facility at Yale to provide technical support for scientific and biomedical computing. He was also co-Director of the Interdepartmental Neuroscience Program at Yale from 1993–1999. This was a critical period for the INP, a time when its inter-departmental nature was being questioned and before the program had an independent training grant. Haig Keshishian (Professor of Biology and currently INP co-Director) volunteered the following thoughts when he learned of Murdoch's death: '*Murdoch's abiding approach to education was to place the interests of his students first. In practice this is much easier to say than to do. Running a very unusual graduate program that cut across departmental boundaries certainly appealed to Murdoch. I sensed a certain rebellious glee in his Scottish accent when he found a way to straighten out a student's problems in a fair way, perhaps at the expense of a department's traditions or interests. Fairness, common sense, and decency in his dealings with others characterized the man, and we will miss him.*' I think everyone who knew Murdoch would second this portrayal. Murdoch's positions on issues were always guided by what he thought was right, not necessarily by what was right for him. He truly was the best kind of man – a man of principle.

J Murdoch Ritchie is survived by his wife Brenda, son Alasdair, and daughter Joceyln.

Jim Howe
Professor of Pharmacology, Yale University

David Colquhoun adds:
In 1970, Heinz Schild allowed me sabbatical leave and, on the advice of Humphrey Rang, I went to work with Murdoch Ritchie during the time when he was chairman of the Department of Pharmacology at Yale. It turned out to be the best thing I could have done. His enthusiasm for doing experiments was legendary. This was not a lonely job in a corner of the lab of some distant great man. Despite his being chairman at the time, we were doing experiments together every day. He'd occasionally disappear for a few hours for a meeting, but then he'd be back at the rig. Not only was he there doing the experiments with me, but the experiments were fun. There was a constant stream of jokes between the serious stuff. At the time I was single, and it was pretty obvious that it was not entirely coincidence that every rotation student in the lab was female. Murdoch seemed to get a lot of fun from speculating about my progress with them (and I had a lot of fun letting him speculate). He and Brenda Ritchie (née Bigland) could not have been better

hosts. I spent a lot of time at their lovely house in Deepwood Drive, and the only price that was exacted was to help with the mammoth leaf-sweeping job in the Fall. His competitive streak was also very much in evidence when playing Scrabble in his Vermont log cabin (actually rather large and luxurious). Luckily, he was very good at Scrabble.

The first thing I had to do when I arrived was to buy a car, and I found a demonstration Mustang Convertible at a good price. This sparked Murdoch's considerable competitive streak, and very soon he had gone out to buy the new model, on the grounds that nobody could have a newer model than the chairman. I tried to keep a straight face when, a bit later, he left the brake off and his new model rolled into a lake. On one unforgettable occasion Murdoch drove me into the lab, in the middle of winter, with the top down, his large scarf blowing in the wind. We took an indirect route so he could demonstrate skidding on the icy road. An article about him appeared in a Yale magazine with the title 'the Flying Scotsman'. The title could not have been more appropriate.

We were trying to measure the density of sodium channels by measuring binding of tritiated tetrodotoxin and saxitoxin, quite a novel method at the time (use of radiolabelled molecules for binding measurements had been introduced only 5 years earlier, by Paton & Rang, 1965). Later it turned out that our values were not very accurate because of poor radiochemical purity of the ligands, but it was a start on a problem that Ritchie and others later brought to perfection.

The project raised some interesting theoretical problems too. The rate at which binding approached equilibrium was, we suspected, not limited by the rate of binding to receptors, but by diffusion, slowed by concurrent binding, in the desheathed rabbit vagus nerves that we used for most experiments. Numerical solution of the non-linear partial differential equations for diffusion with binding was done on the Yale mainframe IBM. A comma missing in the program meant bringing back your corrected box of punched cards and handing it in to the computer operators so you could collect the results next day. Despite his mathematical background, this aspect seemed to interest Murdoch less than dissecting the nerves and getting experimental measurements. He was certainly the most enthusiastic experimenter I have ever met, and his influence on my attitude to science was huge. There could never have been any fraud in Murdoch's lab. He was there, doing things with his own hands.

For many years after my time in Yale, I used in lectures the trick mentioned in Jim Howe's obituary, to demonstrate the denaturing effect of alcohol on proteins. In fact I embroidered it a bit by hiding under the bench a cocktail shaker containing ice and lemon juice: at the end of the lecture the products of the demonstration were poured into the shaker and converted to a whiskey sour. It was the most (possibly the only) popular lecture I gave, and that is yet another reason to be grateful for Murdoch's influence.

Murdoch revelled in the many good things of the American way of life, I don't recall him ever showing any inclination to return to his roots. The only thing that made him seem uncomfortable was politics. If the talk got too political, he'd shift uneasily from foot to foot and the subject was soon changed. Perhaps that was influenced a bit by the fact that only the year before at Yale he had been at the heart of the great student revolts of the late 1960s. He seemed at his happiest in the lab or at a barbecue party. His enthusiasm was infectious, as was his generosity. At the end of my stay at Yale, the first pocket calculator appeared that would do logs and exponentials, the Hewlett Packard HP45. On my last trip into the lab I found a note on my desk. It said: 'the HP45 is in the drawer. If it is not there tomorrow, it won't be missed'. I still have it. I shall miss him.

Richard D Keynes adds:

I collaborated with Murdoch Ritchie for a good many years, and he was my favourite colleague because he was always able to make me feel so cheerful about life!

I first met him when he was still working in London at University College, and he came to help me at Babraham on the permeability of desheathed rabbit vagus nerves to radioactive potassium ions in, I think, 1963, as a visiting Fellow of Churchill College. I knew that he was familiar with such nerves, and hoped that my boss at the ARC would regard rabbits as authentically agricultural, unlike the squid on which I was always more likely to experiment. The handsome white rabbits that we used were also very good to eat, though I am afraid that we soon

Murdoch Ritchie in Northern Italy (1989), after a meeting on peripheral nerve.

saturated the Institute's taste for them. We got together at intervals to work on permeability problems several times after that, but our most memorable research project was to measure the temperature changes in the olfactory nerves of pike during nervous activity, these fishes having exceptionally small nerve fibres with a favourable surface to volume ratio for such measurements. For this purpose we went to Switzerland, where a good supply of living pike was available in the lakes on the estates of the wealthy gentry in the country, and our very good friend and colleague Alex von Muralt was an eminent physiologist at the University of Berne, who knew everyone ready to supply us with a pike. This led, in 1975, to the publication of a paper by Howarth, Keynes, Ritchie and von Muralt on the heat production associated with the passage of a single impulse in a pike nerve, which was possibly the last work to be done on this particular problem, as described in a review by Keynes and Ritchie in *Quarterly Reviews of Biology* in 1985. My only regret was that I happened to be away on the great day when my colleagues reported that the unfortunate pike had been delivered at the university with all the impressive pomp usually restricted to the arrival of royalty!

I last worked with Murdoch Ritchie 10 years later on the binding of labelled saxitoxin to a squid axon, for he was said to be famous in the USA for having persuaded their Central Intelligence Agency to allow him in 1975 to use this very poisonous neurotoxin for labelling sodium channels in physiological experiments instead of destroying it as dangerous, as had been suggested by President Nixon. It did indeed become a very useful agent for use by neuro-physiologists.

The cult of statistical significance

How the standard error costs us jobs, justice and lives
By Stephen T Ziliak & Deirdre N McCloskey
The University of Michigan Press. 352 pp, £18.50
ISBN 0472050079

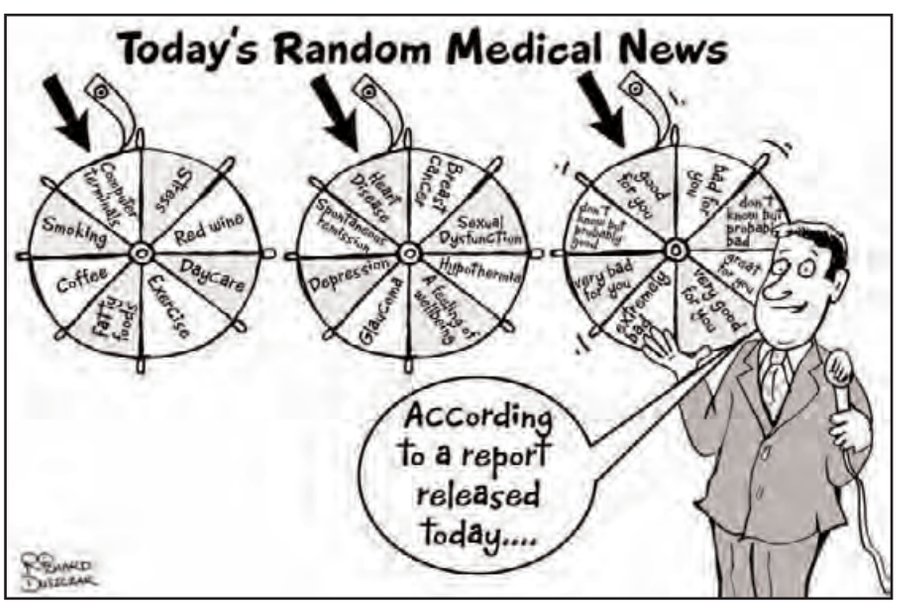
The tenet of this book, zealously delivered by the authors, is to forego statistical significance in favour of substantive significance. Rather than seeking the statistical Rubicon of $p < 0.05$, instead use quantitative judgement to draw your conclusions from experimental results. This focus on the quantitative dimension (or oomph as named by the authors) is reiterated throughout the book, with numerous examples to illustrate the point. Although the authors are economists and a large proportion of the book is devoted to this field, the strategy they advocate is universal and equally applicable to the life sciences.

The first two chapters are heavy going indeed, and the middle section only eases up slightly in highlighting the statistical crimes committed in the fields of economics and psychology, but the last 50 pages or so are the most interesting to the casual reader, relating the contributions of Gosset and Fisher to statistical testing. This is in fact the main point of the book – how Fisher manipulated Gosset's t distribution (*Physiology News* **71**, 13–16), foisted the $p < 0.05$ upon an unsuspecting public, and used his influence (and enormous intellect) to quash any dissent.

In essence what Fisher did was to create a statistical black box into which experimenters would input their data and the results would come out the other end with no thought required by the experimenter. Data either were or were not significant and that was that. How different this is from Gosset's view where careful experimental design and good considered judgement were of prime importance.

It is unlikely a life scientist would seek out this book in preference to a standard statistical textbook. The main obstacle the book presents is not based on statistics, but rather the style of writing, which is full of dreadful puns, a staccato delivery that is infuriating and the occasional haiku thrown in for light relief. What the book is crying out for is a chapter in which the equations related to all the calculations/tests described in the text are illustrated and appropriate example data used to demonstrate key points. Without this the relevance of the standard error of the title may not be immediately apparent. As such this book can never hope to appeal to the casual reader. The changes in statistical reporting demanded by the authors would require a monumental shift in the editorial policy of journals, and the authors direct their pleas to journal editors and individual experimenters alike. The great pity I found in this book is that the message, which is blindingly obvious to those who have considered the use of statistics applied to experimental data, is blurred by the obtuse text. The authors' website tells us a forthcoming study of Gosset is in the pipeline, which should be of more interest to readers of this publication.

Angus Brown



Oxford handbook of transcranial stimulation

Edited by Eric M Wassermann, Charles Epstein, Ulf Ziemann, Vincent Walsh, Tomas Paus and Sarah Lisanby. Oxford University Press, 748 pp, £59.95
ISBN 978-0-19-856892-6

This book is a well organized collection of chapters by experts in the field of transcranial magnetic stimulation (TMS). It is divided into six sections, the first of which gives excellent detail on the physics and biophysics of TMS. The next four sections deal with: TMS measures of cortical and corticospinal excitability; motor-evoked potentials in health and disease; TMS in perception and cognition; TMS and brain mapping.

The final section of the book discusses the therapeutic applications of TMS including its use in depressive and anxiety disorders, schizophrenia, bipolar disorders and movement disorders. It is here that the true potential of the technique becomes fully apparent, particularly as a recent phase III clinical trial (O'Reardon *et al*, 2007) has shown TMS to be effective in treating major depression with minimal side effects, thus offering clinicians a possible alternative to medication in the long term.

The book is well written and edited and should become a standard reference work for those interested in TMS and its uses.

Bill Winlow

Reference

O'Reardon JP *et al* (2007). Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. *Biol Psychiatry* **62**, 1208-1216.

King's College London
Vascular and smooth muscle physiology Themed Meeting
15–17 December 2008

The international panel of speakers includes

Stephanie Lehoux (McGill Division of Experimental Medicine, Quebec, Canada)
Dynamics of shear stress-induced remodelling

Qingbo Xu (James Black Centre, London, UK)
Stem cell differentiation into vascular cells induced by mechanical stress

Per Hellstrand (Lund University, Sweden)
Stretch-dependent growth and differentiation in vascular smooth muscle

Paul Cahill (Dublin City University, RoI)
Bio-mechanical activation and notch signalling – how vascular cells respond to stress!

John Tarbell (The City College of The City University of New York, USA)
Mechanotransduction and the glycocalyx

Gerard Nash (University of Birmingham, UK)
Modulation of inflammatory responses of endothelial cells by changes in local shear stress

Cormac Taylor (University College Dublin, RoI)
Regulation of gene expression by hypoxia

Axel Pries (Charité-Berlin, Germany)
Intergration of haemodynamics and molecular factors in vascular adaptation

Akos Koller (Semmelweis University, Hungary)
Mechanotransduction of shear stress and regulation of microvascular resistance

Stuart Egginton (University of Birmingham, UK)
Haemodynamic forces as* in vivo *angiogenic stimuli

Robert Reneman (Maastricht University, Netherlands)
Wall shear stress distribution in the arterial system. Reconsiderations based upon* in vivo *measurements

Peter F Davies (University of Pennsylvania USA)
Endothelial phenotype plasticity in unstable flow regions of the cardiovascular system: Differential microRNA expression

Shu Chien (University of California, USA)
Effects of shear flow on selectin expression in endothelial cells co-cultured with smooth muscle cells

Robert Krams (Imperial College London, UK)
Shear stress, inflammation and atherosclerosis

Ann Canfield (University of Manchester, UK)
Engineering vascular grafts

Gary McVeigh (Queen's University Belfast, UK)
Waveform analysis and microcirculatory function

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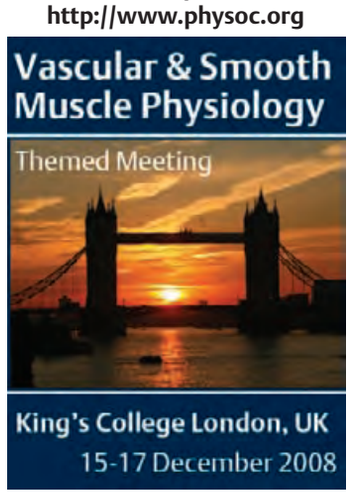

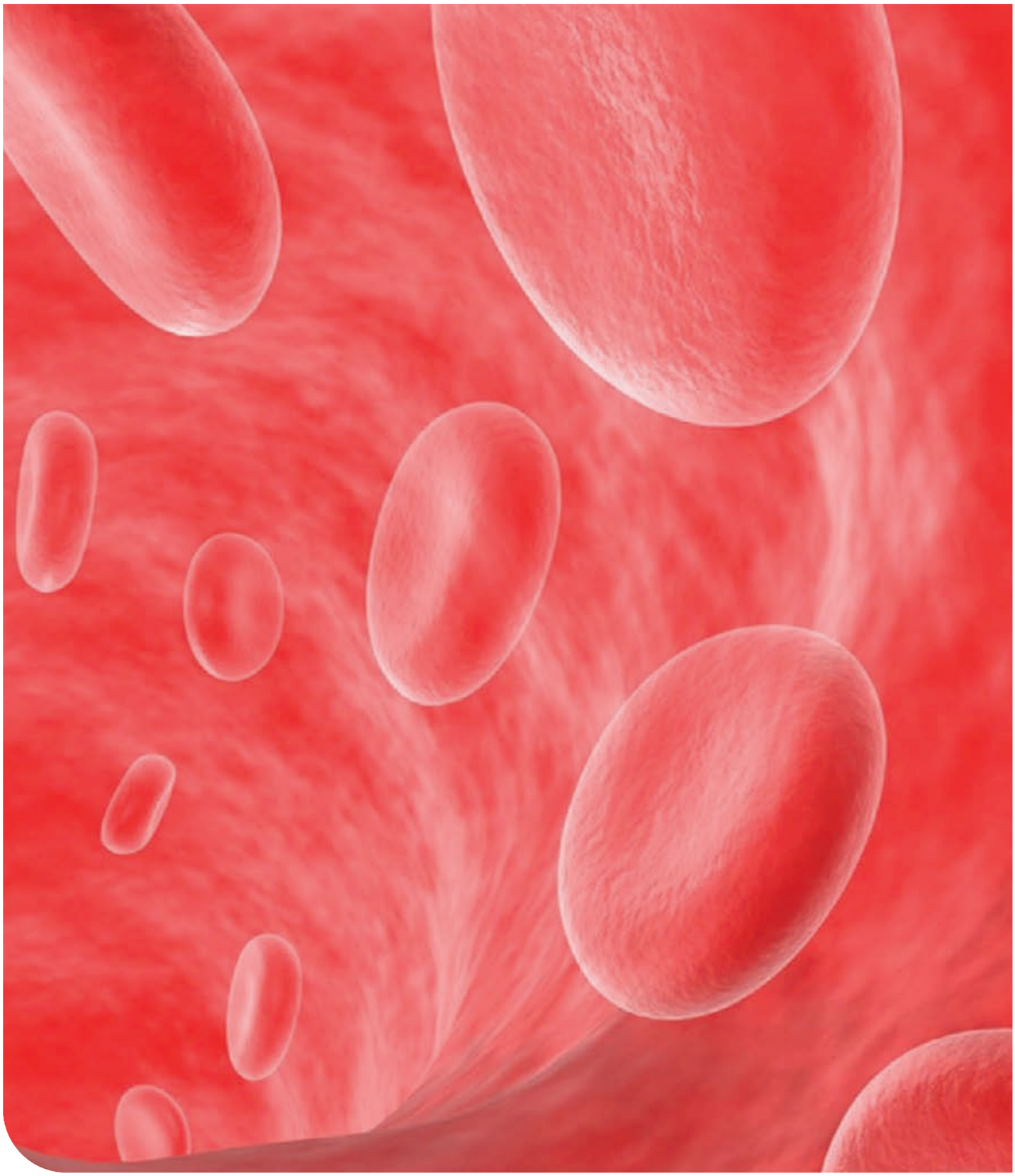

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