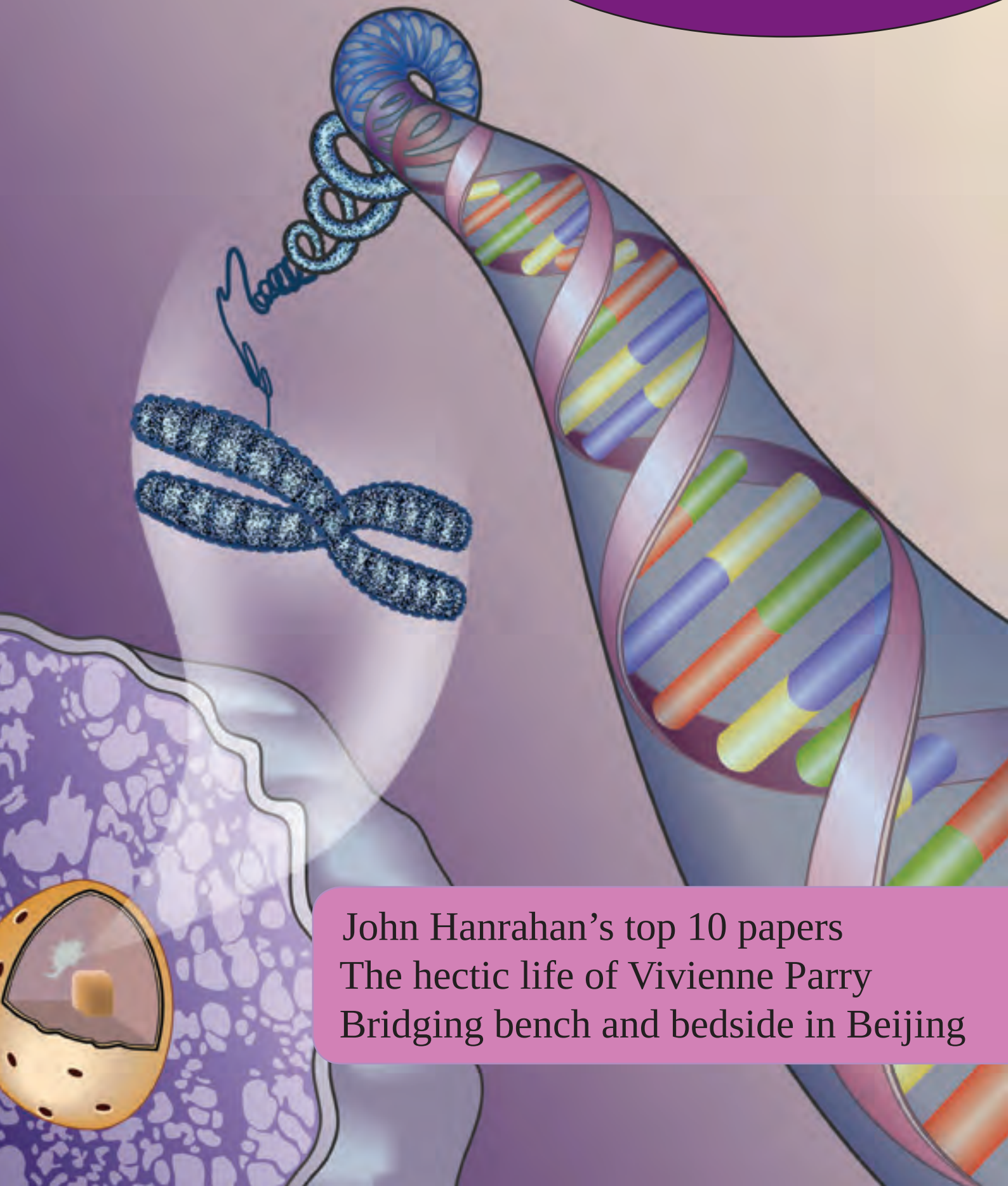
PHYSIOLOGY NEWS

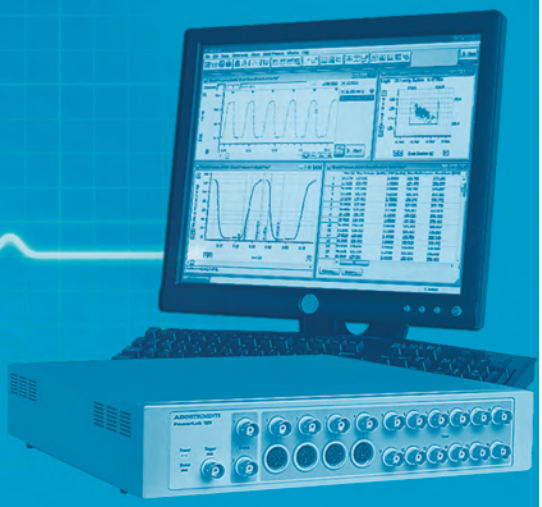
spring 2009 I number 74



John Hanrahan's top 10 papers

The hectic life of Vivienne Parry

Bridging bench and bedside in Beijing



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

Published quarterly by The Physiological Society

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ISSN 1476-7996

The Physiological Society is registered in England as a company limited by guarantee: No 323575. Registered office: PO Box 11319, London WC1X 8WQ.
Registered Charity: No 211585.

Printed by The Lavenham Press Ltd

Advancing the science of life

Cover image from *The Journal of Physiology* Symposium *Physiological regulation linked with physical activity and health*

PHYSIOLOGY NEWS

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Action points

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

Membership applications
Applications for membership to The Physiological Society are considered on a rolling basis, and a decision is normally made within 15 working days. For full information, 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 Summer 2009 issue, No. 75, should reach the Publications Office (jberriman@physoc.org) by **4 May 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).

In this issue

Welcome to the Spring 2009 *Physiology News*.

A highspot of many physiology undergraduate courses, and a perennial favourite with students, is 'physiology at the extremes' and the related topic of physiological adaptation. For an example of the sweep of such topics, Dino Giussani takes in the high Andes, Cambridge and the womb in three pages (p. 24). Elsewhere it turns out that exercise, which seems to be good for almost every bit of you, is beneficial for your liver (p. 31) as well as your cardiovascular system (p. 27).

Adaptation, both short and long term, handily exemplifies the need for understanding at both a molecular AND a systems level – systems biology, if you prefer. Alistair Mathie offers an interesting perspective on physiology and systems biology in his report from the recent Beijing Meeting (p. 9). We also have a wide range of features and news, including our North American Correspondent John Hanrahan's Ten Key Cystic Fibrosis Papers (p. 14), and a glimpse of the life of science writer and broadcaster Vivienne Parry (p. 18), while for an overview of all the Society news, see the Chief Exec's Foreword on p. 4.

Finally, on a personal note, this issue marks the last one for which we have the services of our peerless Executive Editor, Linda Rimmer, who is retiring after six and a half years with *Physiology News* and a total of 22 years working on the Society's journals. The smooth production of *Physiology News* over Linda's tenure bears testament to her unflustered organisational skills – especially since she has had to contend for most of it with the challenge of working with me, an Editor invariably in desperate need of organising. All of us on the *Physiology News* editorial group wish Linda a long and happy retirement. She will be a hard act to follow.

Austin Elliott
Editor

The last time

Just before Christmas, UK physiologists in the universities found out how they, their departments, and their universities, had done in the 2008 Research Assessment Exercise (RAE 2008). Well, sort of.

The results revealed were 'quality profiles' for the submitted 'units of assessment' (UoAs) – the opacity of the jargon is telling, though probably all too familiar to UK-based readers. There had been (as usual) considerable 'gaming' as universities decided which category/UoA to submit groupings of staff in. There also seems to have been far more PR applied by individual universities to the interpretation of their own results than in previous Exercises – a current joke has it that there is no university in the UK whose website is *not* hailing their stunning achievements in RAE 2008.

To some extent, this reflects the fact that the Exercise has borne out the high quality of most university research in the UK. At a time of economic near-meltdown, with many businesses in crisis, the higher education sector remains one of the UK's greatest successes on the world stage.

Getting down to how individual universities fared, more dispassionate analysis generally reveals the biggest research players at the top of the overall rankings, in much the way, and even the precise order, that commentators had predicted. *Research Fortnight* summed this up with: 'RAE shows excellence but little movement'.

One key piece of the picture has been missing. What the results actually add up to is unclear in probably the most critical respect – the financial outcome. The financial formulae that will be used to translate the 'Quality profiles' into the block grant that universities receive from the public purse to support research are to be announced in early March, almost exactly as this issue reaches you. 'Word on the street' is that there has been much behind-the scenes lobbying, as different parts of the university sector try to ensure they do not lose out.

A cynical view would thus be that the whole RAE exercise achieves little apart from telling us what we already knew – UK university research remains high quality, and comparatively cheap, Universities occupy a broadly understood research pecking order – and maintaining the *status quo* via a share out that always broadly reflects 'share of the current research pie'. Of course, it is probably true that to see which institutions have truly moved up, or down, the pecking order, one needs to take a view that spans several, or all, of the six RAEs since the first one in 1986.

Which brings us to the final point – this is the last ever RAE. It is to be replaced by a different exercise, the 'Research Excellence Framework' (REF), which will not require universities to compile detailed written submissions but will use some yet-to-be-agreed basket of statistics and metrics. It seems highly unlikely, to say the least, that agreeing on what this is to be will be a straightforward task. The RAE has, throughout its life, retained its central element of expert peer review, a process academics are broadly comfortable with. How peer review will feature – if at all – in the REF is unclear. The RAE, almost universally unloved and routinely derided as a bureaucratic nightmare, has driven repeated waves of often unpopular departmental mergers, and has attracted opprobrium for fostering short-termism and distorting research priorities. But the trepidation about its successor suggests the RAE may yet be remembered in rather the same manner as in Churchill's oft-quoted line about democracy: 'It has been said that democracy is the worst form of Government – except all those others that have been tried'.

Victories – and a challenge

I have written before in the editorial column about the feeling many scientists sometimes have of science being under threat from a resurgent tide of belief-based nonsense.

One of the reasons for drawing attention to this was to highlight the dangers of simply putting our heads in the sand, and hoping it will all go away. The oft quoted (though possibly apocryphal) remark often used to summarise this is the one attributed to Edmund Burke: 'All that is necessary for evil to triumph is for good men to do nothing'.

In my personal view scientists should, collectively and individually, get more involved in trying to promote rational thinking, as well as wider scientific understanding – and, of course, in combating irrationality and ignorance. A particularly pernicious trend is the rise in nonsense masquerading as science, or 'Cargo Cult Science', in Richard Feynman's pithy description.

Even if we do not get involved personally, we should support and acknowledge those on the front line. It is therefore a pleasure to note that the last few months have seen a couple of notable victories.

One was the campaign launched by Voice of Young Science, which garnered a lot of media attention in the UK in early January with its well-argued and punchy campaign exposing the utter lack of science behind most claimed 'detox cures' or 'detox regimes'. You can read more about their work on p. 56.

Another success was the announcement, by the University of Salford, that it was discontinuing its 'Bachelor of Science' degrees in Complementary Medicine-related subjects. This follows the earlier announcement that the University of Central Lancashire was suspending its programmes of this kind – including a BSc in Homoeopathy – pending a full-scale review.

It bears clarifying what was actually being objected to about these kind of courses. As David Colquhoun – who I would call our unofficial'Point Man' on combating anti-science – has argued repeatedly, the objection is to badging as science things which are overtly unscientific, as in not based on critical assessment of evidence. This is emphatically *not* an attack on academic freedom, as some have claimed. The study of beliefs is a legitimate academic subject, but unless the approach is broadly scientific – founded in the scientific method – it is not science. Degrees teaching, as received truth, a set of beliefs underlying a complementary therapy should be labelled as something else – practitioner diplomas, for instance. But not science degrees.

Meanwhile, it seems clear to me that the place where we most need to be promoting the scientific method is in schools. I would encourage Society Members doing work with schools to centre what they do on the use of the scientific method – empirical hypothesis testing, and the necessity of eliminating confounding factors and subjectivity. Whether you use Galileo's experiments on gravity, the 1988 Benveniste homeopathy affair in *Nature*, or the idiocy of detox regimens, no matter. Just keep stressing how the search to make measurements as non-subjectively as possible underpins all science. And if you will forgive me yet another quotation, remember this one from Mahatma Gandhi: 'You may never know what results come of your action, but if you do nothing there will be no result'.

Austin Elliott

Society update – from the Chief Executive

The Society has ambitious aims for the coming year. We plan to increase membership numbers and to improve the benefits we provide. To do this, we are adding a new member of staff to the membership team; this will allow us more time to actively promote The Society and its membership opportunities at universities and beyond. Increased travel grants are available this year to Members and include grants for undergraduate associates. There are also new international grants available to Members and non-Members of The Society to support junior and senior physiologists from abroad to visit the laboratories of Society Members. The David Jordan International Teaching Fellowship gives recipients an opportunity to visit another institution in order to develop or acquire teaching methods in physiology.

On the educational front, we are contributing to a Practical Biology website aimed at schools (www.practicalbiology.org). Three Young Physiologist Symposia are planned and a Young Life Scientist event, with the Biochemical Society, the British Pharmacological Society and the Genetics Society (see Noticeboard opposite).

Reports of some recent educational activities, including the annual conference of the Association for Science Education and the Life Science Careers Conference 2008, can be found on pp. 49–50 of this issue of *Physiology News*. I attended the Careers Conference (although I am not looking for a new job!) which was ably organised by Chrissy Stokes and Irrum Magre. I was particularly impressed with the way in which Irrum commanded the attention and interest of ~200 students for her CV clinic, despite the fact that they had been listening to lectures all day!

The scientific meetings we organise are a key activity that our Members value highly. In October last year we welcomed Sarah Barnsley as our newly appointed UK Events Co-ordinator. Some of you will have already met Sarah at the themed meeting at King's last year (co-incidentally she has a degree in Human Biology from King's). Sarah has an impressive background in science administration and conference production from her previous jobs at The Ludwig Institute for Cancer Research and Informa Life Sciences and will be a great asset to our events team. There are reports on some recent meetings in this edition of *Physiology News* and articles on upcoming meetings at KCL, Woods Hole and University College Dublin (see pp. 5, 6 and 13). (See the Noticeboard opposite for details of upcoming meetings.)

The way in which we scrutinise abstracts for our Main Meeting has been the subject of an energetic debate within The Society (see *Physiology News* **72**, 47–48). In order to assess the opinions of the membership in the most democratic and inclusive way possible, an online survey of Members was conducted last year. The results of this survey are now on the website and show that there is clearly a spectrum of opinions across the membership of The Society, but that a majority of those responding favour retaining the current system of vetting.

This year we are establishing new initiatives to support our women Members and Affiliates in developing their careers. A new mentoring scheme will pair young women physiologists with experienced mentors from another institution or company, with whom the mentee can discuss their career progression and from whom they can seek advice on a wide range of topics. Valerie Gladwell from Essex University, and Daniella Riccardi from Cardiff have generously agreed to co-ordinate the scheme, which was launched in February.

As a Society it is important that we communicate effectively with the media and the public to explain the importance of physiology. Consequently we are sponsoring a new outreach programme on the brain and neuroscience for schools and the general public at Bristol University during Brain Awareness Week (18–22 March).

Later this year we will be joining Sense About Science's (SAS) Voice of Young Science Programme, which will enable our young scientist Members and Affiliates to attend media training workshops throughout the UK.

And finally, some good news from the financial crisis. The Society is expecting to receive its deposits with the Icelandic Bank Kaupthing Singer and Friedlander back through the financial services compensation scheme shortly. Our Finance Manager will then deposit the money under his mattress as it's the safest place these days !

Mike Collis

Society Notice Board

Upcoming deadlines for Scientific Meetings – 2009

For a comprehensive overview of all your Events News visit the website

King's College London, UK (1–3 April)

Human & Exercise Physiology Themed Meeting

Registration is still open

Woods Hole, MA, USA (9–13 Sept)

Joint International Meeting with the Society of General Physiologists on Basic biology and disease of muscle

Abstract submission and registration opens on 1 February

Physiology 2009 – University College Dublin, Republic of Ireland (6–10 July)

Abstract submission and registration opens on 1 March. For updates visit http://www.physiology2009.org/

University of Newcastle, UK (6–8 Sept)

Epithelia & Membrane Transport Themed Meeting

Abstract submission and registration opens on 22 June.

Young Physiologists' Symposia

Sheffield (6–7 April)

Physiological signalling: from genes to function

Dublin (7 July)

Muscle physiology: function and dysfunction

Leicester (23–24 Sept)

Ion channels and receptors in cell physiology

Young Life Scientists Symposium

Bristol (14 May)

Neurological disorders: from molecules to medicine - Incorporating the Promega UK Young Life Scientist Awards

2010

Physiology 2010 – University of Manchester (30 June to 2 July)

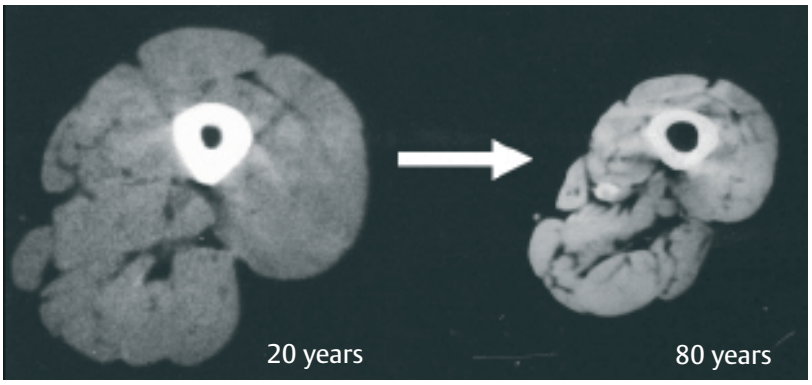
Travel Grants

http://www.physoc.org/grants

New international grant schemes: http://www.physoc.org/international

The ageing musculoskeletal system

Physiological Society Themed Meeting at King's College London (1–3 April)

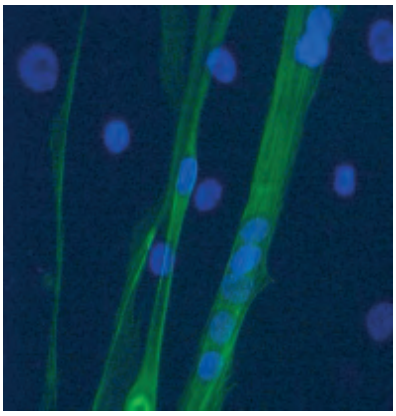


In the face of an increasing proportion of older people in the population, research into ways of maintaining physical independence is a high priority. Adequate musculoskeletal function is crucial to physical independence and therefore to develop appropriate strategies for this and subsequent quality of life we need to better understand how ageing affects our muscles, tendons and bones.

The aim of this meeting is to bring together leading researchers in basic and clinical disciplines related specifically to this field. The meeting will take a multidisciplinary approach, from cellular and molecular perspectives through to the functional relevance of changes throughout the spectrum of whole body physiological performance, i.e. from hip fracture survivors to master athletes. Eighteen eminent national and international experts will lead several topic sessions: Mechanisms underlying sarcopenia, metabolism and contractility of aged muscle, ageing bone and tendon, adaptation to exercise and maintenance of physical independence. In conjunction, young scientists will present their work through oral and poster communications.

This is the first Human & Exercise Physiology themed meeting. King's has been recognised for many years for having a strong tradition in human physiology with a considerable number of members of the Human Physiology Special Interest Group having undertaken the MSc programme in Human & Applied Physiology.

Delegates to the meeting will have the chance to sample the delights of Borough Market and all that central London has to offer in springtime. With dinner on HMS Belfast and many excellent local restaurants and bars, the meeting should provide an enjoyable forum for discussion.



Whist the focus is on ageing, the breadth of disciplines will interest members from other SIGs in addition to Human Physiology and may also appeal to those without a specific focus on ageing. All are welcome. Online registration closes 29 January and full details are available at http://www.physoc.org

Steve Harridge
Carolyn Greig

Meeting Organisers and Human Physiology SIG Convenors

Speakers

Tom Kirkwood (University of Newcastle, UK)
William Evans (University of Arkansas for Medical Sciences, USA)
Mike Rennie (University of Nottingham, UK)
Anne McArdle (University of Liverpool, UK)
Stephen Harridge (King's College London, UK)
Roger Woledge (Imperial College, London, UK)
Giuseppe D'Antona (University of Pavia, Italy)
Jamie Timmons (Heriot Watt University, Edinburgh, UK)
Jonathan Reeve (University of Cambridge, UK)
Tim Skerry (University of Sheffield, UK)
Michael Kjaer (University of Copenhagen, Denmark)
Janet Lord (University of Birmingham, UK)
Hans Degens (Manchester Metropolitan University, UK)
Per Aagaard (University of Copenhagen, Denmark)
Marco Narici (University of Manchester, UK)
Roger Enoka (University of Colarado at Boulder, USA)
Taina Rantanen (University of Jyväskylä, Finland)
Dawn Skelton (Glasgow Caledonian University, UK)

Muscling in to Massachusetts!

Welcome to the Joint Meeting with the SGP. Woods Hole, 9–13 September 2009

Have you ever been to Woods Hole and Martha's Vineyard? Located on Massachusetts' Cape Cod, Woods Hole is a classic New England seaside setting. Sailings from dockside go to the old sea captains' island of Martha's Vineyard, visible across the sheltered water of Vineyard Sound. Home to some of the most famous and richest people in America, this is also the beautiful location of the Woods Hole Marine Biological Laboratory (MBL), and the home of the US-based Society of General Physiologists (SGP). Founded at the MBL in 1946 by researchers working on squid axons and sea urchins, SGP, the parent society of the Journal of General Physiology (JGP), still holds its annual meetings in Woods Hole.

In September 2009, SGP and The Physiological Society will hold a joint meeting, over 4 days, at the MBL. Why should you go? Well, scientifically, the organizers (David Eisner and Lee Sweeney) are putting together a first rate and diverse program 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. There will be invited speakers, as well as short talks drawn from submitted abstracts and posters. Secondly, as a British scientist living in the US, I am well aware that most American society meetings tend to be very big, very impersonal and, especially for young people, can be very difficult to navigate. SGP happens to be a relatively small Society (about 600 members currently), and traditionally embraces the same overall interests as The Physiological Society. In this meeting, the Phys Soc is an equal participant with SGP and so perhaps for the first time ever in North America, Phys Soc will have a real presence, and the meeting should be small enough and friendly enough for all.

But aside from the scientific and professional side of the meeting, this is really 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 (22–27ºC), and the sea is warm enough to swim in at night through the amazing phosphorescent algae that are present in the lagoons. A ferry boat ride to Martha's Vineyard or a dedicated whale-watching trip make for a non-standard Phys Soc 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. And of course there is always the international city of Boston, for some sophisticated night life en route, if you need it!

To really make you feel at home, there are genuine Phys Soc-style accommodations with single beds in the MBL dorms but, for the well-heeled, local inns and B-and-Bs can provide charming and upscale alternatives. Woods Hole is about 90 minutes by car or coach from Boston's Logan airport, which is served by several daily flights from the UK.

So please take a look at the SGP website (http://www.sgpweb.org/), then start making plans to join us for what promises to be a fantastic meeting, and if you have any ideas or questions about the meeting, don't hesitate to contact David, Lee or myself!

Colin Nichols

Beijing Physiology 2008

After a period of planning that involved some interesting time zone-complicated email correspondence between a number of international physiological societies, a Joint International Meeting was held in Beijing from 19–22 October 2008. The meeting represented the efforts of five physiological societies to create a new format for international meetings in which each society contributed to the scientific programme and provided financial support for its own participation. The participating societies in Beijing Physiology 2008 included the Chinese Association of Physiological Sciences, The Physiological Society (UK), the American Physiological Society, the Canadian Physiological Society, and the Australian Physiological Society. In addition, the meeting was co-sponsored by the International Union of Physiological Sciences (IUPS), the Federation of the Asian and Oceanian Physiological Societies (FAOPS), and the National Natural Science Foundation of China. Following fairly soon after the excellent Olympics, held in China just a few weeks previously, Beijing Physiology 2008 was seen as a great success by all participating societies and a major step forward towards greater future interaction with the shared approach to hosting meetings seen as beneficial to all societies, both scientifically and financially.

The theme of Beijing Physiology 2008 was *Physiology in medicine: bridging bench and bedside* and, whilst perhaps seen as a hackneyed theme by some, the conference organisers made every effort to be true to the theme with a series of symposia that addressed the implications of physiological research upon human health concerns in the 21st century. Attendance at sessions was high throughout the meeting, discussions both formal and informal were lively and our Chinese hosts, especially the ever willing students who helped with all operational aspects of the meeting from registration to ordering taxis (quite tricky, as you can imagine – but the cheapest way for UK delegates to travel, at least once a fare had been pre-arranged!), were wonderful in ensuring everything ran smoothly. My treasured possession from the meeting is a bright orange 'helper's t-shirt' that the students ordered specially for the visiting organisers. Although produced at the largest size possible, I don't think I'm the only one who can only wear one whilst breathing out! A Chinese XXL isn't the same as a UK one, obviously!

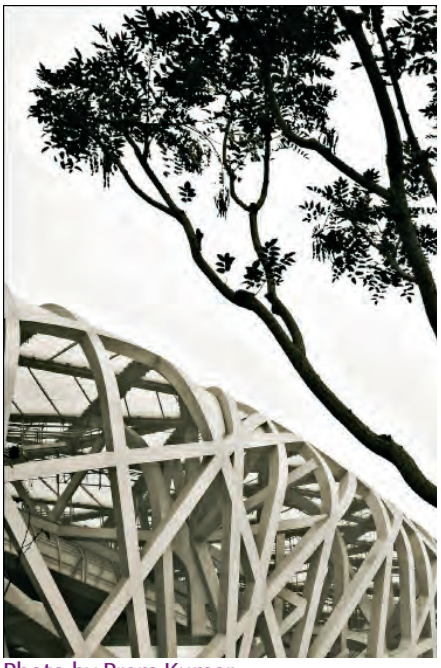


Photo by Prem Kumar.

Beijing Physiology 2008 was a truly successful endeavour. Held at the Xijiao Hotel and Conference Center, the meeting attracted 605 delegates. There were 407 full delegates (Mainland China 157; Australia 11; Canada 27; UK 58; USA 88; 66 were from other countries and regions) and 198 students (Mainland China 145; Australia 3; Canada 15; UK 11; USA 6; 18 were from other countries and regions). There were representatives from 35 countries at the meeting, with a total of 592 abstracts received. Among the abstracts, there were 3 from invited plenary lectures, 80 from invited symposium speakers, 7 from young physiologists' symposium speakers, 21 free oral speakers and 482 posters as determined by the Scientific Organizing Committee of the conference. In addition, there were 27 exhibitions during the conference: 17 were from companies based in Mainland China and 10 from outside China.

In advance of the scientific sessions, the APS and The Physiological Society conducted a workshop on 'How to get your work published in English-language biomedical journals and trends in Western biomedical publishing' (see the article by David Nicholson for more details, p. 12). In planning for BP 2008, it was felt that the workshop was timely given the rapid acceleration of scientific productivity in China and the desire of many Chinese authors to publish in Western journals. Such a session would be of value to many physiology students and early career scientists and it is my aim to timetable similar sessions into our main meetings where possible. The Chinese participants were particularly keen to learn how to publish in high impact journals – and The Society's journals were very well regarded in this respect.

Language was not a particular barrier, with almost all Chinese students at the meeting being able to hold detailed conversations in English. It was clear, however, that they were less able to follow some of the talks when delivered quickly and I found it interesting to note how the digital camera was finding use as a means of recording entire Powerpoint deliveries! My Mandarin, unfortunately, was limited to just a few words but I think just making an effort to say hello/thank you was always graciously received – even though it must have sounded terrible to their ears!

For Western scientists attending BP 2008, Sunday night was the start of their orientation to Chinese hospitality. The meeting organizers arranged for a wonderful welcome reception with samplings of Chinese foods. On Monday morning, Xian Wang (Secretary-General, Chinese Association of Physiological Sciences

(CAPS), Peking University), opened the session and welcomed the meeting participants. Her greeting was followed by one from Ming Fan (President of the Conference and CAPS). Representatives of each of the participating societies then followed with their own welcoming comments. Our President, Clive Orchard, spoke on our behalf – to thank the hosts and to welcome the collaborative venture we were about to undertake, making comparisons to the Beijing Olympics in the shared aim of achieving excellence and friendship.

The Physiological Society was privileged to have Denis Noble as the opening keynote lecturer, presenting a talk on Principles of systems biology from a physiologist's perspective. The talk was based on an article resulting from the Paton Lecture he delivered to the LifeSciences2007 meeting in Glasgow in July 2007 with the principles derived from his superb book on systems biology, The Music of Life (Noble, 2006). Denis generously agreed to take questions and we were all thrilled to hear some debate between him and some die-hard reductionists in the audience! Two additional plenary lectures were presented during the meeting. Shu Chien (UCSD, USA) presented Mechanotransduction and vascular biology and Ming Fan

(Institute of Basic Medical Sciences, Beijing) presented Advances in hypoxic physiology in China. These two were both excellent – but differed in many ways; Shu Chien's state of the art fundamental, cellular and molecular research contrasting with Ming Fan's more applied and basic studies aimed at preventing human fatalities during the building of the world's highest roads and railways. Note to self: if your breath hold time in seconds does not exceed your mean resting heart rate (bpm), then don't consider climbing any mountains in retirement!

The 16 symposia offered at BP 2008 each generally included speakers from at least three of the participating societies. In addition, the organizing committee put together three free oral sessions on cardiovascular and cellular physiology, regulation of ion channels, and metabolism, renal and endocrinology. The meeting also included one Young Physiologists' Symposium. These four sessions were designed to encourage the participation of scientists submitting volunteered abstracts to the meeting. As a Chair of one of these sessions I was very impressed by the quality of the science and the delivery – not one talk ran over time. The major difficulty – one not unique to China – was in trying to encourage young scientists in the audience to ask questions of the speakers. It was at the posters these that the younger scientists were able to be more engaging. The enthusiasm of the presenters was very encouraging, the quality of the posters was generally very high and all participants seemed genuinely pleased to receive any feedback.

The banquet was held on Tuesday evening and was a typical Chinese feast with multiple courses and numerous toasts. In addition, the local organizing committee arranged entertainment which included dancers performing the Peacock Dance, a short performance of the Beijing Opera, martial arts dancers called Gongfu, and a performance by a Chinese mask changer. In addition to the formal entertainment, a number of physiologists volunteered or were coerced to sing songs from their home country. While the amateur entertainment started with an offering from Tai Yao (Past President, CAPS) – an Elvis cover, if I remember correctly – it ended with a duet of New York, New York sung by Kim Barrett and Hannah Carey (University of Wisconsin). In between, the UK made some valiant attempts – but I am sworn to secrecy by many of those involved – although I think Richard Naftalin deserves special mention here for most unexpected solo artist of the night! At some point we all ended up on stage singing Auld Lang Syne! Phys Soc rules exclude voting so no winners were announced.

In closing the meeting on Wednesday afternoon, the representatives of the participating societies heaped praise on the Local Organizing Committee and our Chinese hosts for their hospitality and friendship and for offering the international community a scientifically exciting meeting. Many of our Members took the opportunity to visit Beijing and the surrounds – with the ancient delights of the Forbidden Palace and the Great Wall competing with the ultra-modern Birds Nest Olympic Stadium for space on their memory cards and neurones.

Prem Kumar

Meetings Secretary

Special thanks to Martin Frank (Executive Director, American Physiological Society) for kind permission to use some of his summary of the meeting.

Physiology and systems biology: clear voices rise above the noise in Beijing

October last year saw the first Joint Physiological Sciences Conference– a joint initiative by the Physiological Societies of China, Australia, Canada, the USA and the UK. The programme and symposium speakers sounded inviting and I'd never been to China before, so, a trip to Beijing in October seemed like fun. I still feel a bit of a truant going off to a meeting during term time, but, in truth, all my commitments for that week were relatively easily rearranged or delegated.

Considering the number of countries involved, attendance was a little disappointing, although, having said that, there were plenty of pertinent presentations and enough like-minded scientists and old friends and colleagues to have interesting conversations with, during breaks and over dinner. I find myself, these days, often comparing attendances at meetings unfavourably with the 30 000 plus numbers at, say, the annual Society for Neuroscience meeting in the US. I can't say, though, that I've ever managed (or had the inclination) to talk to more than, perhaps, a couple of hundred neuroscientists at any one such meeting and so, from my perspective, I suppose the rest are really just occupying potential seats in bars and tables in restaurants.

Anyway, back to Beijing and the meeting. The city itself was an experience; much larger than I'd anticipated and, for a pedestrian as I was, the traffic is a nightmare. It is almost impossible to cross roads without taking evasive action on the way, and one quickly has to develop a thick skin as indicator lights are uniformly replaced by the liberal use of the horn. Nevertheless there are some stunning sights and places to visit, my favourite being Beihai lake and park just north of Tiananmen Square and the Forbidden City. Moreover, the pollution I'd been warned about was mostly cleared

The Qinghai–Tibet Railway.

by October breezes and cooler temperatures.

Culturally, the experience that sticks most in my mind, however, is the accepted behaviour of the audience at the meeting itself during talks. A cacophony of cameras, mobile phones, conversations with neighbours, conversations with long lost friends across the hall, shouting matches with unidentified recipients on the other end of the phone, texts being sent (loudly) and received (even more loudly) – nothing was interrupted by the minor inconvenience of listening to, or letting others listen to, the hapless speaker at the podium. For those of us out-with the front couple of rows, in order to see many of the slides in full, we had the additional task of leaning wildly from side to side throughout presentations to navigate the constant to-ing and fro-ing of youthful helpers struggling with outsized pots of tea and ensuring that the privileged few sitting at the front were never thirsty.

Scientifically, for me, the most memorable contributions to the meeting were two plenary lectures on the mornings of the first and

second day; the first by Denis Noble of the University of Oxford and the second by Ming Fan of the Institute of Basic Medical Sciences in Beijing, who was also the conference president. What made these lectures special is that both speakers had a message that they wished to impart, rather than simply use the opportunity to remind us of work done by endless hordes of post-docs and students in their respective labs over the last 20 or so years, as is often the form for such talks. Denis Noble's message seemed, to me, to influence the tenor of the whole meeting, but more of that later. The second plenary by Ming Fan was a treat. Ming Fan's grasp of English, although infinitely better than my knowledge of any Chinese, is, by his own admission, not great. He tackled this by using a range of stunning slides with minimal description. Ming Fan's area of expertise is classical hypoxic physiology. He brought the topic to life with a montage of pictures taken from the Chinese plateau region, an area of the Chinese mainland of stunning beauty with an average altitude of 4500 metres (~15 000 feet) which makes up 16% of the total land mass. Thus, for the population that lives there and anyone who wants to visit (or work, or study there), altitude sickness associated with hypoxia is a real issue. Additionally, there are many local medicines from the region that are used to alleviate both acute and chronic altitude sickness – a fertile area for study, then, for both physiologists and pharmacologists alike.

Ming Fan described his involvement in the construction of the Qinghai–Tibet Railway, the world's most elevated railway, the final phase of which (the Golmud–Lhasa section) was completed in 2006. Eighty per cent of this astonishing 1142 km section of the line is at an altitude above 4000 m and train carriages are designed with an oxygen supply for each passenger. Before construction began, a 1% mortality rate was estimated for working continuously at such a high altitude, which gave an alarming prediction of 1300 worker deaths during the

5 years of construction. Ming Fan and his team managed to persuade the Chinese government to divert substantial resources to himself and his colleagues (the experts in hypoxia research in China) to monitor worker health and performance and suggest steps to be taken to minimise risk to the workers. As a result, the railway was built with no worker fatalities and much valuable research material has been obtained. I've no idea how he managed this success, but even in a language he was not particularly comfortable with, his engaging manner and force of personality shone through in this plenary lecture. The real message behind Ming Fan's talk was an impassioned plea for further resources to be committed to this area of research and, at least as important, for more students who want to enter the field, rather than continue to be seduced by the perceived quick gains in the current fads of molecular and structural biology. I hope he succeeds.

In this regard, Denis Noble's talk a day earlier raised similar issues and I was struck by how many subsequent speakers throughout the meeting echoed the same thoughts and even altered their presentations to acknowledge Noble's influence on their thinking and future planning. In many ways his talk served as a clarion call: it is time for physiology, in the form of systems biology, to reclaim lost ground (and lost funding?) and reassert itself as a primary 'player' in biological and medical sciences research. If this is to happen, there are two issues that need to be addressed. First, how does physiology assert itself as the study of systems biology? Second, what is the way forward for physiologists to advance the science of systems biology?

Following an affectionate introduction from Tai Yao (Fudan University), Denis Noble attempted to answer both of these questions in an intellectually demanding yet stunningly eloquent plenary. I can't begin to do justice to Noble's complex, multifaceted lecture here in a way that wouldn't make it appear facile. Instead, I can only tell you how I interpreted it and explain my thoughts on the topic then and since. Everything that follows is my own take on the subject, so if I have misinterpreted Denis Noble's message, the fault is entirely mine.

In the first part of his talk, Noble summarised his 10 principles of systems biology (his '10 commandments' if you like). These are principles of systems biology seen very much from a physiologist's perspective. He described that while the science of molecular biology and

Paul Fraser, Clive Orchard and Prem Kumar, enjoying the hospitality.

the cloning of the human genome transformed thinking in the decade before and around the turn of the millennium, systems biology is the true science of the 21st century. The problem, of course, is that systems biology is remarkably ill-defined; it means entirely different things to different people.

Noble believes that since the work of Claude Bernard in the 1860s, physiology can stake a claim to be the true science of systems biology. At present the field is dominated by molecular and cellular biologists who believe that you can only understand how a system works by first understanding how the component parts work. This is a reductionist view of biology and, as an unreconstructed reductionist myself, it is largely my view too.

The central dogma of molecular biology is that information flows in one direction, from DNA to RNA to proteins and so on up through cellular mechanisms, cells, tissues, organs and the organism. However, this view is clearly incomplete. For example, whilst RNA determines what protein will be made it does not determine how much will be made.

Noble raced through his 10 principles, illustrating how 'genes do nothing on their own' and 'DNA is not the sole transmitter of inheritance'. He showed examples of downward causation and that 'higher level controls of gene expression and triggers of cell signalling' exist, as do processes of feedback control.

As an electrophysiologist, I was easily persuaded by his example regarding computer modelling of the pacemaker rhythm of the heart, an example based on Noble's own research interests. Similarly, I am conscious that cardiac fibrillation doesn't work at the cellular or molecular level; no individual ion channel can be regarded as the primary pacemaker, and we need to understand the higher level control of the rhythm of the heart. However, I can accept that these examples alone might not sway others who work in different research areas.

This is ground that Noble has clearly covered many times before, indeed I had heard much of the same story at the Life Sciences conference in Glasgow in the summer of 2007 (see Noble, 2008). Nevertheless, it was delivered with such alacrity and with such a hearty confidence in the philosophical background of the audience (misplaced in my particular case – I once again had to do some 'homework after class' to reaffirm my understanding of the term Lamarckism – the inheritance of acquired characteristics) that it was no bad thing at all to be re-acquainted with this background in order to benefit more from the second part of the plenary. Following his Glasgow talk, I was sufficiently inspired to rush out and buy Noble's book '*The Music of Life*' on the topic (Noble, 2006), but after both the lecture and reading the book I was left feeling somewhat deflated. Whilst I could buy into the idea that reductionism is not the panacea, I remained completely unclear as to exactly how physiologists could re-invent themselves as systems biologists in a way that would allow

us to design meaningful experiments that would yield convincing interpretable data to further the field.

A positive interpretation of this (and this is Noble's interpretation) would be that higher levels in biological systems impose boundary conditions on the lower levels. Without understanding those conditions and their effects, we will be seriously restricted in understanding the logic of living systems. My view, in the past, has been more negative: if we don't understand how the basic building blocks work (the individual molecular entities, if you like) or even what these basic blocks are, then we'll have little chance of understanding and interpreting the system. I was left struggling to be convinced that making things more complicated by adding even more potential variables would help.

If I'm totally honest, my approach has been largely to ignore these extra levels of complexity, or perhaps even worse, look for instances where I can find evidence that they occur (G protein regulation of ion channel activity, for example) and exploit it as an interesting phenomenon for study and publication, without really putting the process into the context of all the other regulatory pathways that may be acting simultaneously. My fall-back is that I don't know whether other processes exist or what they might be but, of course, that doesn't mean they aren't happening *in vivo*.

In Beijing, Noble, an enthusiastic orientalist, extended his talk from Glasgow by the clever use of analogies with China – both Chinese language and Chinese medicine. For me, this worked extremely well on a number of levels. It engaged the home audience (some even stopped texting, momentarily) and provided, to my mind, some clear examples of how physiologists (and pharmacologists) might actually contribute to systems biology on our own terms.

For example, Noble referred to written Chinese and pointed out that there are around 40 000 characters that are used time and time again to

make up the full written language. In many ways, these characters are analogous to gene modules which are used again and again for many different functions throughout the body. Thus, genes can be thought of as linguistic metaphors. To me, this was a thoughtful and useful analogy.

Similarly, Noble suggested that there is an interesting parallel between systems biology and oriental medicine. Oriental medicine is patient oriented and often looks for multiple methods of treatment. In a similar way, systems biology looks for multiple actions that regulate and control a particular function. It was suggested that a systems biology approach might aid the developing field of patient-specific medication.

Finally, Noble returned to his own research and his work with the anti-anginal drug ranolazine and its potential additional use as an anti-arrhythmic agent. This compound is efficacious as an anti-arrhythmic agent in the heart because it has multiple targets. At a therapeutic concentration, ranolazine blocks both the cardiac persistent I_{Na} and the cardiac I_{KR} current. This combined action is particularly useful in conferring anti-arrhythmic activity, but would have been almost impossible to derive from studies solely carried out at the level of individual molecules.

Thus, a systems biology approach (used by Noble and his colleagues) has furthered the development of a potential novel clinical use for a drug with multiple sites of action, that can, perhaps, be used at lower than usual concentrations. This has analogies with Chinese herbal medicines which often have multiple actions on several targets and, as a result, may be used at relatively low concentrations.

Just occasionally these analogies were stretched too far. For example, Noble stated that acupuncture is sometimes better than drugs in the clinical treatment of headache pain. Whilst some published studies show interesting effects of acupuncture on pain, I'm not convinced the evidence is strong enough to be quite so dogmatic about the value of acupuncture just yet (see Ernst, 2006).

Also, Noble felt it was important not to forget that systems biology must be based on an evidence-based approach, which is not necessarily the case for oriental medicine as it currently is practised. As such, systems biologists must avoid the perception problem faced by oriental medicine where it is often seen by its recipients as nothing less than 'magic'.

As I see it, what Noble is trying to say is that we don't actually need to understand the minutiae of all the building blocks (and indeed we will never reach a point in time when we do), but we do need to concentrate on the important ones. The only way to understand which are important is to study the bigger picture – the whole system. Whilst this is an empirical approach, it may be that we can reduce things to, perhaps, a few hundred important systems of differing levels of complexity – say, 'hearing', 'the cardiac action potential', 'a pancreatic B cell', 'the kidney', 'learning and memory' (OK, that last one is a step too far) and the system will inform the molecular. I'm more taken with this idea after listening to Noble's Beijing plenary and I sensed that many others at the meeting were too, judging by

conversations afterwards and the many referrals to Noble's lecture in subsequent presentations.

Since listening to this plenary in October (a couple of months ago now as I write this), I have begun to get a sense of how I might use systems biology thinking to inform and guide my own research. I still think of experiments, primarily, at a molecular or cellular level, but I'm conscious that I'm more alive to the issues raised by the higher control of the expression and function of the proteins I study, and how this will impact on them. I'm not yet a 'systems biologist' however. I don't have too many clear ideas of how to study (and, more importantly, get meaningful results from) the processes that interest me at a higher level. I'm scared off a little, by the potential number of variables in experiments that would follow from the hypotheses and theories I have come up with to date. I'm not worried though. I've got quite a bit more serious thinking to do yet, for, as Noble states, 'seeking theories is the biggest challenge for systems biology'. While systems biology is not rocket science, it is probably every bit as intellectually demanding.

It is not very often that one gets the chance to attend a meeting and listen to two plenary lectures that have such a profound influence on the subsequent proceedings, and on one's own thinking. Despite the mobile phones, it was a pleasure to be there.

Alistair Mathie

Medway School of Pharmacy, University of Kent. Chatham Maritime, Kent, UK

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Beijing photos by Clive Orchard.

Authorship seminar for Chinese scientists. How to get your work published in English-language biomedical journals and trends in Western biomedical publishing

In October last year I was delighted to join representatives of The Physiological Society and the American Physiological Society (APS) to run a seminar focused on the publishing needs of Chinese scientists. The seminar took place alongside the Beijing Joint Conference of Physiological Sciences and attracted over 150 participants, ranging from students to junior post-docs.

Kim Barrett, Chair of the APS Publications Committee, opened proceedings with a talk entitled '*Getting your work published – telling a compelling story*', and addressed key topics such as manuscript preparation and submission. I followed Kim's talk with a description of the support that authors can expect from publishers such as Wiley-Blackwell, and how we work with their manuscripts from acceptance, to publication and on to 'life' after publication. Marty Frank, Executive Director of the APS, then discussed recent trends in biomedical publishing from the perspective of a major society based in North America.

Ian McGrath presenting on best practice in publication and experimental ethics.

Participants in the afternoon 'tutorial' session.

The presentations in this first part of the seminar then turned back to the practical and ethical issues faced by authors with talks from two members of The Physiological Society. Ian McGrath addressed ethical best practice, covering both publication ethics e.g. plagiarism, and experimental ethics. The session finished with a presentation from David Sheppard on how to work with editors and reviewers, building on the principles described by Kim.

This mix of overview and practical advice worked well, laying the ground for a more hands-on, problem-solving session in the afternoon. The participants split up into groups of 10–12 people guided by experienced facilitators, and worked through a series of practical exercises using handouts provided by the APS. The level of interaction was excellent and the session could easily have run on past the scheduled close of the seminar. Feedback on the day and in subsequent correspondence has underlined the importance of these tutorial-like sessions, particularly amongst more junior participants who are often intimidated by the prospect of asking questions in English, in a crowded seminar room.

The seminar was a great success, giving excellent profile to the societies and publisher, and helping a new generation of physiologists.

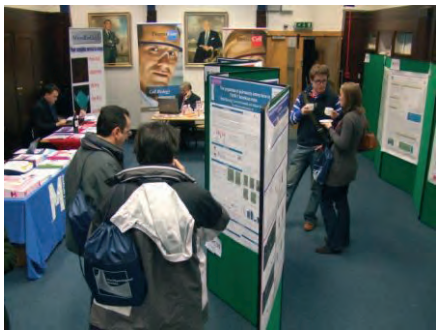
David Nicholson

Journals Publishing Director, Life Sciences Wiley-Blackwell, Oxford, UK

Stress and strain in the vascular system goes down well!

A Vascular and Smooth Muscle Physiology Themed Meeting was held at the Guy's Campus of King's College London, from 15–17 December 2008. The meeting was organized by Maggie Brown (University of Birmingham) and Richard Siow (King's College London), co-convenors of the Microvascular and Endothelial Physiology Special Interest Group. The focus of the meeting symposium – *Vascular responses to mechanical stress: Cellular crosstalk and integration* – was designed to bring together vascular and endothelial biologists with a common interest in the mechanical signals sensed by the cells within the vascular wall. This proved to be a popular topic attracting 16 national and international invited speakers, who between them presented exciting and up-to-date research findings on the mechanotransduction of flow, shear stress, pressure and strain in the context of angiogenesis, vascular remodeling, control of vascular tone, inflammation, and stem cell recruitment for repair of the vascular wall. There was also strong emphasis on the intracellular signalling pathways and gene expression that direct cellular responses and a fascinating insight into how this knowledge can be harnessed to engineer endothelial, smooth muscle cells and matrix into the next generation of vascular grafts. The Physiological Society Special Lecture, presented by Shu Chien (University of California, San Diego), was on the effects of shear stress in endothelial and smooth muscle co-cultures, while the Plenary Lecture, given by Cormac Taylor (University College Dublin), was on gene expression in hypoxia and inflammation.

The concept of Themed Meetings has proved a real winner for The Society. The format of a focused symposium interspersed with oral communications and dedicated



Richard Siow and Maggie Brown (left and right) with Blue Riband poster prize winners Xinghua Cheng (King's College London) and Joanna Kur (Queen's University Belfast).

time slots for poster viewing and discussion provides ample opportunity for scientific interaction across interest boundaries and between young and established researchers. This meeting attracted the largest number of registrants and trade exhibitors for a Themed Meeting in recent years, with 16 selected oral and 54 poster communications presented over the two and a half days, yet the atmosphere remained both friendly and informal. Three young scientists were selected to receive The Society's Blue Riband poster prize. The Society dinner was held in the cellars of the 19th century Southwark Hop Exchange, with plenty of festive Christmas spirit that extended to the wearing of party hats, even by the Meetings Secretary!

Feedback from participants about the meeting has been enormously positive and the topic has clearly excited interest as there are discussions afoot about a repeat gathering, possibly in San Diego. Clearly the 'stress and strain' of this meeting were very worthwhile!

Physiology 2009

University College Dublin
(7–10 July)

It was 18 years ago when University College Dublin (UCD) last hosted a meeting of The Physiological Society. In that period Physiology at UCD has undergone profound change. New 21st century buildings house the disciplines of Medical and Veterinary Physiology in place of old 19th century piles. These new schools of medicine and veterinary science have moved from being satellites in disparate parts of the city of Dublin to being at the heart of the main campus in Belfield and within metres of each other. Physiology has always been the basis for the scientific practice of Medicine and common research goals are shared by investigators at the Health Science Centre, Veterinary School and the Conway Institute. In these laboratories, questions of human and animal morbidity are linked to the physiology of the cell through the essential intermediaries of animal models of disease. Please join us for an Irish welcome at UCD in 2009 and a feast of stimulating symposia. (For full details see poster on inside back cover.)

James FX Jones
University College Dublin

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A relaxed and informal conference for PhD students and post-docs involved in muscle research

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Abstract submission closes 15 May 2009

John Hanrahan's top 10 papers on cystic fibrosis

Why did I say yes when asked to choose 10 key papers on cystic fibrosis (CF)? What was I thinking? The field has undergone spectacular expansion during the past two decades, driven by the intense desire to cure this devastating disease and supported by proactive charities and funding agencies. A quick search of the Web of Science (WOS, Thomson Reuters, London, UK) for articles on 'cystic fibrosis' or 'CFTR' yielded 34 727 references, most of which were recent. That is probably 10 times the number of papers I have read in my life, and key articles are scattered throughout the literature because CF combines so many basic and clinical sciences. When some of my favourites were not among the 1704 CF papers that had been classified by the WOS as 'physiological', I found them under headings such as pediatrics (5992 CF articles), biochemistry and molecular biology (3588), experimental medicine (1911) and cell biology (1967). It has been a challenge to pick a few that have been especially influential.

Cystic fibrosis is an autosomal recessive disease which afflicts about 70 000 people world-wide. It is caused by mutations in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR), an anion-selective channel expressed predominantly in epithelial tissues such as pancreatic ducts, intestine, sweat glands, liver and airways. The most common mutation, deletion of a phenylalanine residue at position 508 (ΔF508), causes partial misfolding and retention of the mutant in the endoplasmic reticulum. This results in diminished epithelial fluid secretion, accumulation of viscous mucous, and in the airways, sodium hyperabsorption and a reduction in mucociliary clearance.

The field has been recognized with various awards including the 2007 Nobel prize in Physiology or Medicine to Oliver Smithies, Mario Capecchi and Sir Martin Evans for their development of gene targeting and mouse models of CF and other diseases (e.g. no. 8 on the list), and the Gairdner award to Lap-Chee Tsui, Francis Collins and Jack Riordan for discovering the gene (e.g. no. 4 on the list). Still, all the papers on my list are personal choices that have influenced me and perhaps other physiologists in the field. The number of times each paper has been cited is shown for those who are interested in such statistics, although they are a flawed measure of influence for several reasons.

John Hanrahan.

With similar work going on in many labs and little opportunity to compare results before publication, CF has seen more than its share of controversy. Of course papers don't have to be correct to be highly influential, but I would prefer to leave discussion of those until I reach retirement, or to be really cautious, the final stage of some terminal illness. Anyway, articles that seem refuted often turn out to be partly correct, so for now I will focus on the ones that have found some consensus and let the dust settle on the others. Important early papers had to be left out even though they set the stage for those on my list. For example, the association of gastrointestinal and airway defects by Guido Fanconi in 1934, CF pancreatic symptoms and the susceptibility to heat prostration by Dorothy Andersen between 1938–1951, and elevated salt content in CF sweat by Paul di Sant'Agnese in 1953 were all turning points. Interested readers are referred to an excellent historical review of these and other highlights (Quinton, 1999). My list also doesn't include recent CF papers that will probably influence physiologists in the future, but they will have to wait because I was only allowed 10.

1 Frizzell RA, Field M & Schultz SG (1979). Sodium-coupled chloride transport by epithelial tissues. *Am J Physiol Renal Fluid Electrol Physiol* **236**, F1–F8 (706 cites)

I lead off with an influential editorial review which summarized evidence for a model for chloride secretion that had been proposed based on studies of shark rectal gland (Silva *et al*. 1977), cornea (Klyce & Wong, 1977) and CF-affected epithelia such as trachea and colon. According to this scheme, transepithelial secretion is limited by the chloride conductance of the apical membrane, which is the site of regulation (Fig. 1). This paper was especially important for me because it also summarized the evidence for sodium-coupled chloride absorption across vertebrate epithelia, and most of my graduate student years were spent trying to show that insects use a different mechanism that does not involve sodium co-transport.

2 Quinton PM (1983). Chloride impermeability in cystic fibrosis. *Nature* **301**, 421–422 (462 cites)

I still remember reading this paper in the library during my postdoc at Yale. It showed that there is a defect in chloride conductance in CF, and this could explain why CF sweat is salty. The sweat gland has two main parts, a blind-ended secretory coil and a reabsorptive duct that modifies the fluid as it flows to the skin surface. Both parts are affected, but a micropuncture study by Irene Schulz in CF had already shown that high salt results from abnormal

transport in the duct (Schulz, 1969). This paper by Quinton got me and other chlorophiles excited by showing a decrease in Cl^- permeability, which serves as a shunt during electrogenic Na^+ reabsorption. Isolated ducts were perfused with different salt solutions while measuring the transepithelial potential. The lumen was –6.8 mV in control ducts when the lumen and bath solutions contained 150 mM NaCl, but was –76.9 mV in CF ducts! A similar hyperpolarization was observed when control ducts were perfused with Na_2SO_4. The inability to reabsorb Cl^- as a counter ion for Na^+ provides the basis of the sweat test that is still used clinically for diagnosis. If only all results could be so clear-cut.

3 Gray MA, Greenwell JR & Argent BE (1988). Secretin-regulated chloride channel on the apical plasma membrane of pancreatic duct cells. *J Membr Biol* **105**, 131–142 (163 cites)

As the patch clamp technique found its way into epithelial labs there was great interest in identifying the chloride channel that might be abnormal in CF. An outwardly rectifying chloride channel had been identified in cultured epithelial cells and there was much excitement that it might mediate secretion and be defective in CF but this paper by Gray *et al*. on native epithelial cells was the first to suggest another candidate with lower unitary conductance and little rectification. After several years of trying unsuccessfully to replicate cAMP regulation of outwardly rectifying anion channels in primary cultures and with tenure review looming, Joe Tabcharani and I began frantically patch clamping T84 cells, a well-established model for cAMP-stimulated chloride secretion. We only found cAMP activation of a distinctive little channel like the one reported by Gray *et al*. in pancreatic duct (Tabcharani *et al*. 1990), and our conclusion about its role was reinforced by work from the Lazdunski lab describing a similar channel in stimulated thyroid cells (Champigny *et al*. 1990). This paper had a profound effect on my research, especially after massive numbers of the same channel appeared in insect cells when they were made to express the CFTR gene (Kartner *et al*. 1991).

4 Riordan JR, Rommens JM, Kerem B-S, Alon N, Rozmahel R, Grzelczak Z, Zielenski J, Lok S, Plavsic N, Chou J-L, Drumm ML, Iannuzzi MC, Collins FS & Tsui L-C (1989). Identification of the cystic fibrosis gene: Cloning and characterization of complementary DNA. *Science* **245**, 1066–1073 (3729 cites)

I came to the CF field from zoology in the 1980's during the exciting 'race for the gene' and was amazed to find groups working neck-and-neck on the same problem. This was one of three back-to-back articles by the same group which completely changed the field by showing that the mutated gene in CF encoded a membrane protein related to those that mediate solute transport in bacteria and multidrug resistance in mammalian cells, now called the 'ATP binding cassette' or 'ABC' protein superfamily. The gene was identified by positional cloning without knowing its precise function, as reflected by the vague name given to its predicted protein product, the cystic fibrosis transepithelial conductance regulator or CFTR (also the call letters of a popular AM radio station in Toronto, now called 680News). There was much speculation about the function of CFTR because (a) it did not look like any known channels (Fig. 2) and (b) no other ABC proteins were ion channels (it is still unique in this regard. ABC proteins include channel

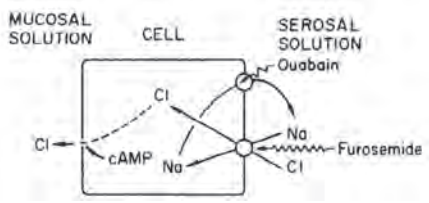

Figure 1. A working model for electrogenic Cl^- secretion induced by cAMP
Reproduced from Frizzell *et al*. (1979) with permission from the APS.

regulators; however, no ion channels have been found amongst the 47 other ABC proteins in humans or the >2,000 superfamily members throughout the kingdoms of life).

5 Cheng SH, Gregory RJ, Marshall J, Paul S, Souza DW, White GA, O'Riordan CR & Smith AE (1990). Defective intracellular transport and processing of CFTR is the molecular basis of most cystic fibrosis. *Cell* **63**, 827–834 (892 cites)

Since the function of CFTR was not known, it was not immediately obvious how mutations might affect its activity. This key paper showed that ΔF508 and several other disease-associated mutations that had been identified in CFTR cause retention of the mutant in the endoplasmic reticulum. The attachment of oligosaccharide chains at two asparagine residues in the fourth extracellular loop requires passage through the Golgi, thus the presence of only immature, core-glycosylated CFTR on Western blots provided strong evidence for this trafficking defect. Many of the other 1603 known mutations in CFTR also probably cause misprocessing but are rare compared to ΔF508, which is on 68% of CF chromosomes worldwide. There was some controversy about whether the channel function is altered by ΔF508, but it is now clear that its responsiveness to PKA phosphorylation is reduced when compared with normal CFTR.

6 Anderson MP, Gregory RJ, Thompson S, Souza DW, Paul S, Mulligan RC, Smith AE & Welsh MJ (1991). Demonstration that CFTR is a chloride channel by alteration of its anion selectivity. *Science* **253**, 202–205 (735 cites)

Its biophysical signature, cAMP regulation and appearance whenever CFTR was transfected into a different cell type convinced us that it was a channel but did not exclude the possibility that it regulates a ubiquitously expressed endogenous chloride channel. This paper, which was the first structure–function

study of CFTR, strongly suggested that CFTR contributes to the pore by showing that mutations in the first and sixth transmembrane segments alter the selectivity of whole-cell currents. Although the determinants of anion selectivity are still not fully understood, subsequent studies have confirmed that these transmembrane segments influence anion permeation (Sheppard *et al*. 1993; Tabcharani *et al*. 1993; Ge *et al*. 2004) and that the front half of CFTR plays a greater role in ion selectivity than the back half (Gupta *et al*. 2001).

7 Bear CE, Li C, Kartner N, Bridges RJ, Jensen TJ, Ramjeesingh M & Riordan JR (1992). Purification and functional reconstitution of the cystic fibrosis transmembrane conductance regulator (CFTR). *Cell* **68**, 809–818 (640 cites)

Mutagenesis and patch clamping showed that CFTR or at least parts of it probably line the pore, but is CFTR sufficient to form a functional channel? This paper answered that question and proved that CFTR is indeed a low conductance, non-rectifying channel which does not require any accessory proteins to conduct anions or be regulated by phosphorylation. CFTR was expressed in insect cells, then extracted with alkali, solubilized using ionic detergent, and purified to homogeneity by column chromatography and gel filtration. When purified protein was reconstituted into phospholipid vesicles then fused with planar lipid bilayers, low conductance channels similar to those seen previously in cells were activated by phosphorylation, firmly establishing its chloride channel function.

8 Snouwaert JN, Brigman KK, Latour AM, Malouf NN, Boucher RC, Smithies O & Koller BH (1992). An animal model for cystic fibrosis made by gene targeting. *Science* **257**, 1083–1088 (511 cites)

This article described the first mouse model for cystic fibrosis. The murine *cftr* gene was targeted by inserting a stop codon and neomycin resistance gene near the site where a rare truncating mutation causes severe CF in humans, effectively knocking out expression of CFTR. Most mice died soon after weaning with severe intestinal obstruction reminiscent of meconium ileus in humans, which occurs in about 10% of CF newborns. Many mouse models of CF (knockouts and transgenics with ΔF508 and other mutations) are now available and our favourite is the hit and run ΔF508 mouse developed by Bob Scholte and colleagues (van Doorninck *et al*. 1995), which we use for studying the effects of potential therapeutics.

9 Hwang T-C, Nagel G, Nairn AC & Gadsby DC (1994). Regulation of the gating of cystic fibrosis transmembrane conductance regulator Cl channels by phosphorylation and ATP hydrolysis. *Proc Natl Acad Sci U S A* **91**, 4698–4702 (197 cites)

The nucleotide binding domains are a conspicuous feature of CFTR and it was shown early on by the Welsh lab that hydrolysable nucleotides are required for normal channel

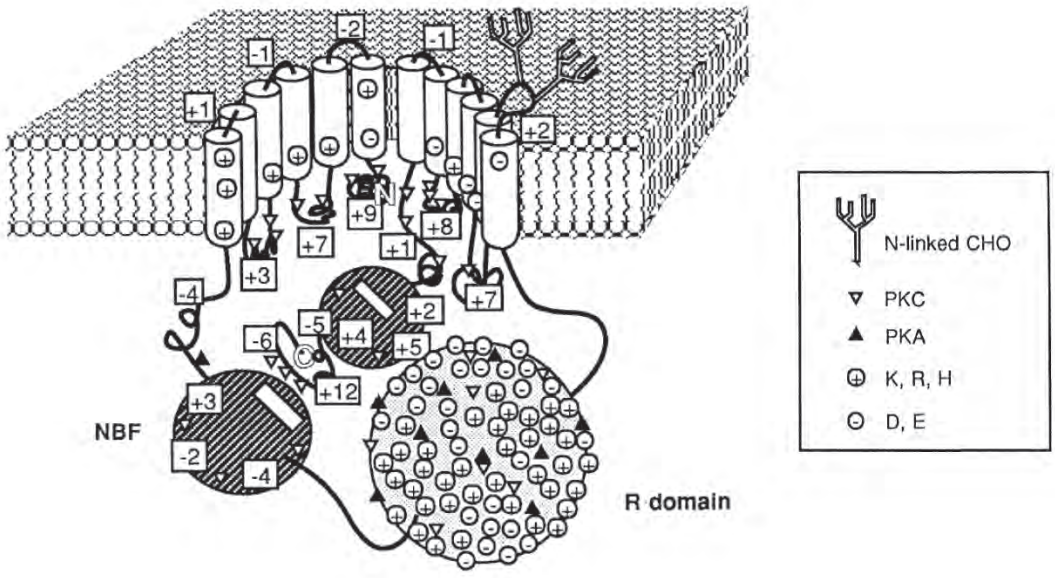

Figure 2. Schematic model of the predicted CFTR protein

The six membrane-spanning helices in each half of the molecule are depicted as cylinders. The cytoplasmically oriented nucleotide binding folds (NBFs) are shown as hatched spheres with slots to indicate the means of entry by the nucleotide. The large polar R domain links the two halves. Charged individual amino acids are shown as small circles containing the charge sign. Net charges on the internal and external loops joining the membrane cylinders and on regions of the NBFs are contained in open squares. Potential sites for phosphorylation by protein kinases A or C (PKA or PKC) and N-glycosylation (N-linked CHO) are as indicated. K , Lys; R, Arg; H, His; D, Asp; and E, Glu. Reproduced from Riordan *et al*. (1989) with permission from the AAAS.

activity, although hydrolysis energy is not required to open the channel (Aleksandrov *et al*. 2000). This study showed that once single channels were phosphorylated and opened by ATP they could become locked in an open burst state by exposure to the poorly hydrolysed analogue AMP-PNP. The locking effect was dramatic and stimulated much excitement about the individual NBDs and their functions. It is now well established from structural studies of other ABC transporters (e.g. Smith *et al*. (2002)) and functional studies (Vergani *et al*. 2005) that the NBDs dimerize and sandwich nucleotides at their interface.

10 Stutts MJ, Canessa CM, Olsen JC, Hamrick M, Cohn JA, Rossier BC & Boucher RC (1995). CFTR as a cAMP-dependent regulator of sodium channels. *Science* **269**, 847–850 (596 cites)

Enough about anions... CFTR can have effects unrelated to its ion channel activity, and although I wouldn't call them functions, they probably have important physiological and pathophysiological consequences. Early work by Mike Knowles, John Gatzy and Ric Boucher showed that the potential difference across the nasal mucosa of CF patients was hyperpolarized (lumen-negative), and this was ascribed to sodium hyperabsorption (Knowles *et al*. 1981). Later studies of airway epithelia confirmed increased Na^+ absorption in CF, in marked contrast to reduced absorption in the sweat duct. This paper was influential because it demonstrated a link between CFTR and sodium transport. Adenoviral expression of CFTR reduced absorption of Na^+ across monolayers of dog kidney (MDCK) cells that had been stably transfected with ENaC, the epithelial sodium channel. Surprisingly, raising cAMP inhibited Na^+ absorption in monolayers that coexpressed CFTR but increased it in cells lacking CFTR, and similar results were obtained in patch clamp experiments with transfected 3T3 cells. The interaction between ENaC and CFTR remains poorly understood and controversial, although recent data indicate that proteolytic processing of ENaC might be involved.

There for now are my top 10 papers, with apologies to authors of the other 34717. Honorable mention goes to two papers that are having profound impact on translational research; Denning *et al*. (1992) with 599 cites and Brown *et al*. (1996) with 194 cites. They provided a rationale for pursuing trafficking correctors as CF drugs by showing that low temperature (i.e. 28°C) and chemical chaperones (e.g. glycerol) can partially rescue ΔF508 CFTR.

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Two months in the life of a freelance science writer and media personality

Vivienne Parry (below) tells us about her hectic schedules ranging from advising the Government on medical issues to teaching communication skills to chemists

There is no typical day for a freelance writer and broadcaster. There is no typical week even. Rather, there is a pell mell of activity and deadline, driven by the news agenda and by constant change. It means there is little structure to my days, and it is almost impossible to plan ahead. When I say that I have no idea what next week holds, people don't quite believe me, but it's true. Some would find this unsettling but I love it. So here is a selection from the last couple of months of 2008.

I have a portfolio career like almost no-one I know. There is writing for newspapers and magazines, as well as reports and websites. There is broadcasting, principally medical science for Radio 4 but also much punditry for other stations and for TV. There is presenting – of films for corporate clients, of conferences and other events. There is involvement with UCL, one of the world's great universities, where I am Vice Chair of Council, with the MRC, where I also serve on their Council and with various other bodies including the Joint Committee on Vaccination, the Medicines and Healthcare Products Regulatory Agency and the Science Media Centre. Work on science and society issues was at the forefront of my work as 2008 drew to a close.

So let's start with the writing. I was writing a column for The Times called 'Behind the Headlines', the premise of which is that there is a science back story to most headlines, particularly the health ones. The subject was given to me on a Thursday at about 11.30 am and I had to deliver 650 words by about 1.30 pm. Sometimes it was something that I had an opinion about or some vague knowledge. Many times I knew as much about it as the man in the street. Occasionally it was utterly daunting as in 'Vivienne, the Mosley trial (Max Mosley was the F1 boss who was the subject of lurid stories in the News of the World) finished this week, can you write about the science behind sado-masochism'.

On average I wrote at least two features of 1200 words a week. Usually I suggest these. Ideas for features come from reading widely, or are sparked by meeting people. I always ask lots of questions! I do a great deal of reading each week for my job; New England Journal of Medicine, Lancet, British Medical Journal, New Scientist and Nature are obligatory, plus three daily newspapers, five papers on Sunday, The Times Higher and sundry other monthlies and books. I read mostly on the underground on the way to and from meetings. But there were commissions too. For instance, in October I interviewed Olympic gold medal cyclist, Nicole Cook who gave me cycling tips and later, Jose Carreras who talked about his leukemia. Nicole Cook rode her lighter-than-a-feather medal winning bike and I rode my trusty sit-up-and-beg with a big basket and I was supposed to keep up with her as we wove our way through heavy London traffic and record an interview at the same time. Dear reader, I failed.

I write and host many programmes for Radio 4. One of the most popular series is 'Am I normal', which started out as a four parter but has now clocked up over 40 programmes. I recorded four more in this award winning series including programmes on memory and miscarriage. The idea is a simple one: take a given subject – say breathing. What's normal lung function? Is normal in Norwich the same as normal in Norway? Who decides what's normal? In this particular case it turns out to be the European Community for Coal & Steel whose original 'normal' population included many heavy smokers. This was because smoking was then the norm. A half-hour programme involves about 2 days of recording interviews and a day of writing and recording the script. I work closely with a producer who does the actual editing and some of the initial research. I've done some awful things to myself in the cause of 'Am I normal'. Treadmills, memory tests, blood sampling, spirometry and even a test to see whether I was just normally bad at maths or had dyscalculia (it was the latter in fact). The worst by far was a stress test where I was made to breathe 3% carbon dioxide whilst some physiologist measured my heart rate and blood pressure. As my body went into panic overdrive, I clung to a single thought: the BBC does not generally allow presenters to die on air.

Another strand of my life is work with the Chief Scientific Officer (CSO) of the Department of Health, who leads the 50,000 healthcare scientists working within the NHS and bodies like the Health Protection Agency. Physiological measurement is a major division within healthcare science. The NHS celebrated its 60th Anniversary in July 2008, so the CSO Conference in November, which I hosted, showcased the work of healthcare scientists over the last 60 years, including the extraordinary advances in hearing tests and devices. I worked too with the Chief Scientist of the Department of

Health (DH), developing the science content of the DH website and with the Department for Innovation, Universities and Skills on the science and society strategy.

I was very closely involved in the report on presumed consent from the Organ Donor Taskforce, which recommended in November that an opt out system should not be adopted at present. Establishing what communications might be necessary should a different system of consent be adopted was the workstream that landed in my lap, along with drafting the report. The final report came out when I was working in Chicago (doing a webcast on personalised medicines) which meant almost no sleep as the entire British media descended on my mobile, paying no heed whatsoever to the 6 hour time difference.

Travel was a major part of October and November. I went to Washington immediately before the Presidential election to give a lecture on risk communication and vaccines, and as mentioned, Chicago immediately after the election when the optimism that Obama's election had generated was palpable. There were trips to Frankfurt, to Paris, to Cannes to launch a major European leukemia initiative, and to Edinburgh to media train a roomful of chemists at the University. Helping scientists to communicate better with the public is something I enjoy enormously.

Physiology was in fact a major part of my degree (Zoology). I loved it but I proved to be a hopeless bench scientist. Everything I touched, broke. I worked for a while with shore crabs, measuring insulin analogues but my lab books of the time are witness to unfolding disaster, with entries like 'No. 17 'Lost', No. 42 'Moribund' and more tellingly still, No. 47: 'Ran away', which was at least proof of intelligence in *Carcinas maenas*. Eventually, after the unfortunate smashing of a large piece of ground glass, I was grounded. UCL refused to let me do any more practicals on the grounds that I had become an unaffordable liability. Today, rather to my astonishment, I am Vice Chair of the UCL Council. I trip guiltily through the porticos on my way to Council meetings, half fearing that those who taught me back then may pop out and denounce me as a complete fraud. Truth to tell, I am daily haunted by Mrs Glass, my Form 1 maths teacher, thinking that she may tap me on the shoulder and say 'What do you think you're up to?', at which point I would meekly say ' Bang to rights ' and slink off quietly. I feel enormously privileged to do what I do, to meet the range of people and to see so much astonishing science at first hand. Life does frequently get a bit out of hand but my enthusiasm is generally undimmed. There are 10 Radio 4 programmes in the diary for 2009 – that much I know – as for what else I may do this year, only time will tell.

Vivienne Parry
Science writer and broadcaster

Survival by downsizing: N-terminal truncation of cardiac troponin T increases heart efficiency during energetic crisis

An example of molecular evolution that adds modulatory structures in proteins is the N-terminal variable region of troponin T in the regulatory system of striated muscle. Recent studies have demonstrated that the N-terminal segment of cardiac troponin T can be selectively removed by restricted proteolysis during myocardial adaptation to energetic crisis. By reducing the velocity of contraction and elongating the time of ventricular ejection, this mechanism suggests a novel approach to developing treatment for congestive heart failure

Actin-activated myosin ATPase powers muscle contraction. In skeletal and cardiac muscles, contraction is regulated by Ca^{2+} via the thin filament-associated troponin–tropomyosin system (Gordon *et al*. 2000). The troponin complex consists of three protein subunits: the Ca^{2+}-binding subunit troponin C (TnC), the inhibitory subunit troponin I (TnI) and the tropomyosin-binding anchoring subunit troponin T (TnT). Three homologous TnT isoforms exist in fast skeletal, slow skeletal and cardiac muscles. These TnT isoforms have conserved middle and C-terminal regions but a highly variable N-terminal region (Jin *et al*. 2008). Biochemical studies have identified that the C-terminal region of TnT binds tropomyosin and interacts with TnI, TnC and F-actin, and the middle region of TnT also binds tropomyosin (Perry, 1998). The N-terminal region of TnT, by contrast, does not bind any known proteins in the muscle thin filament (Fig. 1).

Phylogenetic data have shown that the N-terminal variable region evolved as an addition to the conserved structure of TnT and its deletion does not abolish the Ca^{2+}-dependent activation of actomyosin ATPase *in vitro* and cardiac muscle contraction in transgenic mice. Thus, the N-terminal variable region is considered non-essential for baseline TnT function; however, its presence increases actomyosin ATPase activity and sensitivity to Ca^{2+} activation in reconstituted myofilaments. Though it does not bind other myofilament proteins, the N-terminal variable region of TnT alters the molecular conformation of the conserved regions, and thereby modulates TnT interaction with TnC, TnI and tropomyosin. Studies of intact TnT isoforms differing in their N-terminal variable regions have demonstrated these functional differences (Jin *et al*. 2008).

This functional significance of the N-terminal variable region is supported by its regulation by alternative RNA splicing. A cardiac TnT isoform switch occurs during avian and mammalian heart development, which corresponds to a transition from a more acidic, high-molecular weight isoform to a less acidic, low-molecular weight isoform. The molecular mechanism for this isoform switch is the exclusion of exon 5 that encodes 10 mainly acidic residues in the N-terminal region from cardiac

J-P JIn (left) and Han-Zhong Feng.

TnT (Jin *et al*. 2008). N-terminal alternative splicing is not limited to cardiac TnT. By inclusion or exclusion of multiple N-terminal coding exons, fast skeletal muscle TnT also undergoes an isoform switch during development (Jin *et al*. 2008). In addition, slow skeletal muscle TnT exhibits an up-regulation of the low-molecular weight isoform excluding exon 5 in functional adaptation to certain pathological conditions such as type 1 Charcot-Marie-Tooth disease (CMT), an inherited peripheral polyneuropathy (Larsson *et al*. 2008).

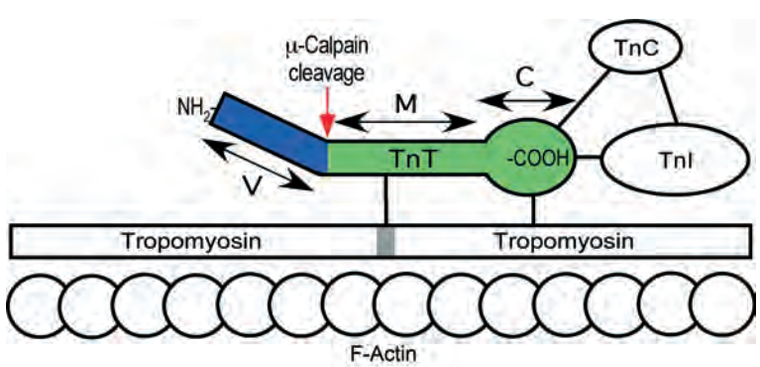

Figure 1. Structure–function relationships of TnT and the N-terminal variable region
Troponin T occupies a central position in the actin thin filament-associated Ca^{2+} regulatory system of striated muscle. Troponin T interacts with TnC, TnI and tropomyosin through its conserved C-terminal (C) and middle (M) regions. The N-terminal region (V) of TnT has hypervariable structure, does not interact with other thin filament proteins, and functions by modulating the conformation and function of the conserved regions. The μ-calpain cleavage site that produces the restricted truncation of the N-terminal amino acids 1–71 is indicated by a red arrow.

In contrast to transcriptional regulation and RNA splicing, proteolysis is a much more rapid mechanism to regulate protein function. For cardiac TnT, we recently discovered that restricted proteolytic truncation of the N-terminal segment occurs during myocardial ischemia–reperfusion (Zhang *et al*. 2006). This truncation of TnT is mediated by μ-calpain cleavage and is a selective removal of the N-terminal variable region (Fig. 1), unlike the caspase-mediated TnT proteolysis which removes the N-terminal variable region together with part of the conserved structure, resulting in significant loss of function (Communal *et al*. 2002). In other words, the calpain-mediated N-terminal truncation of cardiac TnT is regulatory rather than destructive.

Follow up studies confirmed that myocardial infarction in *ex vivo* rat working hearts via ligation of the left anterior descending coronary artery that supplies the anterior wall of the left ventricle resulted in production of the N-terminal truncated cardiac TnT, not only in the infarct but also in remote areas including the right ventricular free wall. This finding suggests an acute whole-organ proteolytic response triggered by regional ischaemia–reperfusion in the absence of systemic neurohumoral signalling. Left ventricular pressure overload in *ex vivo* mouse working hearts produced N-terminal truncated cardiac TnT in both ventricles, further suggesting a role of haemodynamic stress in triggering an acute whole-organ proteolytic regulation (Feng *et al*. 2008).

To investigate the pathophysiological significance of the N-terminal truncation of cardiac TnT under energetic constraint or workload increase, transgenic mouse hearts were created in which the endogenous intact cardiac TnT was partially replaced by N-terminal truncated cardiac TnT. Functional studies showed that the transgenic mouse hearts had decreased contractile velocity and consequently an elongated rapid ejection phase of the cardiac cycle (Fig. 2). Relaxation velocity and ventricular filling time were not affected. These changes would translate into a less powerful heart but also a less energy-consuming pump that is beneficial during energetic crisis. Indeed, when afterload increased, stroke volume decreased in the wild-type but not in the transgenic mouse hearts. The better pumping

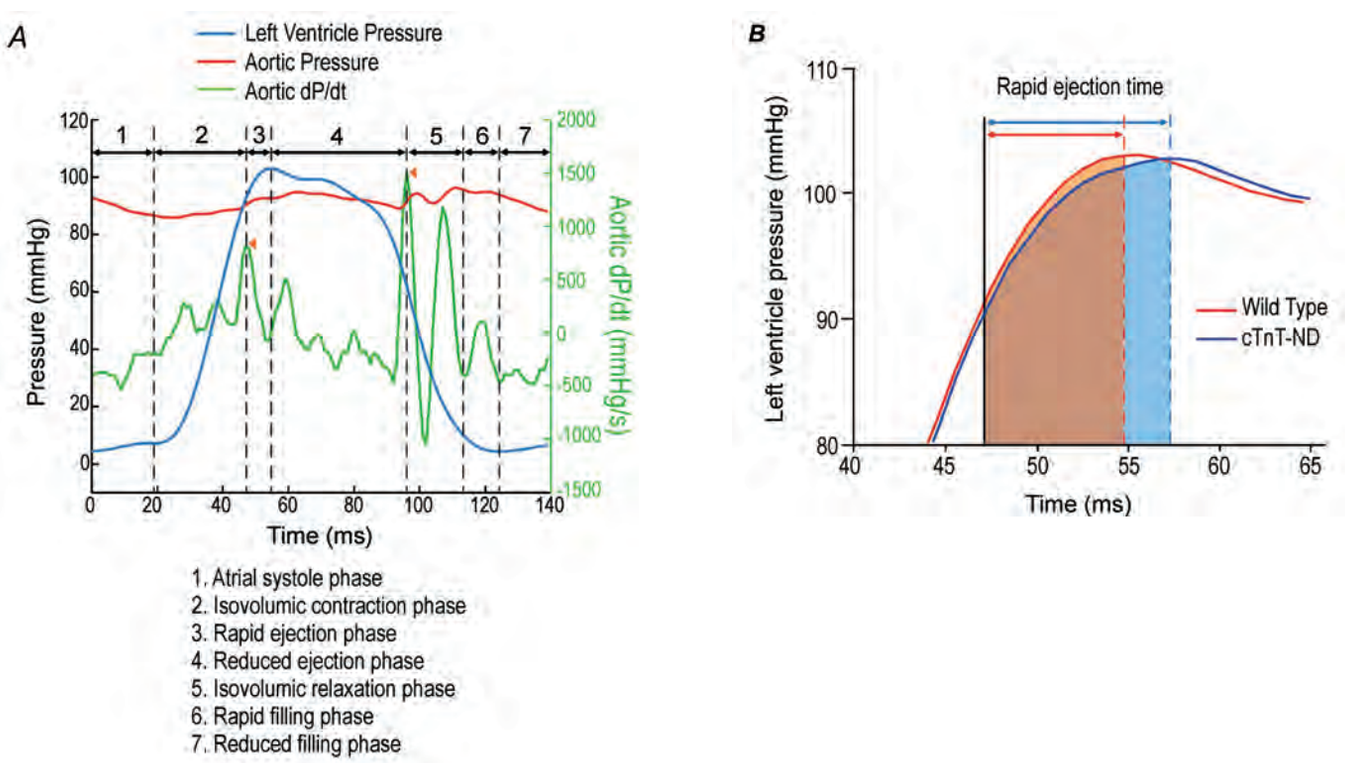

Figure 2. Elongated ventricular ejection time in cTnT-ND transgenic mouse hearts

A, left ventricular pressure, aortic pressure and aortic dP/dt traces were simultaneously recorded in mouse working heart preparations. The functional phases in a cardiac cycle are outlined. The opening and closing of aorta valve were identified by the reversing points of aortic dP/dt trace (indicated by the orange arrowheads). The duration between the opening and closing points represents the ventricular ejection time in which the rapid ejection phase is defined as the duration from the opening of aortic valve to the peak of left ventricular pressure and the reduced ejection phase is from the peak of left ventricular pressure to the closing of aortic valve. *B*, portions of representative left ventricular pressure traces recorded from wild-type and transgenic mouse hearts over-expressing N-terminal truncated cardiac TnT (cTnT-ND) are shown to demonstrate the longer rapid ejection time of the transgenic hearts.

efficiency of the transgenic mouse hearts demonstrates a novel role of N-terminal truncated cardiac TnT in myocardial adaptation to energetic crisis (Feng *et al*. 2008). Although the decreased contractile velocity due to N-terminal truncated cardiac TnT could contribute to the depressed myocardial function in ischaemia–reperfusion, it may provide a protection against Ca^{2+} overload-induced contractures.

Troponin subunits have a rapid turnover rate within cardiac myocytes with a half-life of approximately 3-4 days; therefore, it is plausible that N-terminal truncated cardiac TnT provides a short-term solution for acute ischaemia and other energetic crisis and is replaced with intact cardiac TnT afterwards. In other words, cardiac TnT truncation at the N-terminus seems to switch the cardiac muscle into 'energy-saving' mode to sustain heart function during an acute energetic crisis, which may play a role in cardiac protection.

Switching from the faster α-myosin to the slower β-myosin in mouse cardiac muscle increased energy efficiency of the heart (Hoyer *et al*. 2007). Expression of slower myosin isoforms also increased the energy efficiency of skeletal muscle contraction (Reggiani *et al*. 1997). The finding that the restricted N-terminal truncation of cardiac TnT resulted in slower contractile velocity demonstrated that modification of TnT structure and function could alter myosin cross-bridge kinetics and affect muscle energetic efficiency. The mechanism for TnT to modulate contractile velocity remains to be investigated. Much more also remains to be learned of the cellular mechanisms that regulate this restricted proteolytic modification of cardiac TnT, and more importantly, how these findings can be used to develop new molecular approaches for the prevention and treatment of myocardial deficiency and congestive heart failure. Heart disease is currently a leading cause of death worldwide, and thus our progress in this study, we hope, will hold immense potential and promise in the years to come.

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Acknowledgements

The research discussed in this article was supported by grants from the National Institutes of Health (AR048816, HD044824 and HL078773), the National Aeronautic and Space Administration (NNA04Ck26G), the Arnold and Ann Berlin Cardiovascular Care Research Fund, and The Doberman Pinscher Foundation of America to J-PJ.

Miscellanea

'I found it on Wikipedia ...'

How many readers have ever idly browsed the Wikipedia entries on subjects close to their hearts?

The entry on 'physiology' at http://en.wikipedia.org/wiki/Physiology is brief, dealing only with the general meaning of the word and the history. The latter pretty much stops at the start of the 19th century, though Claude Bernard and Walter Cannon get brief mentions (and links).

The 'physiology' page does give links to both The Physiological Society and the APS, but it is minimal by comparison to the entries for, say, biochemistry or molecular biology. These two are admittedly rather methodological, but also give a lot more useful links to other related sites (e.g. 'Lists of biochemists' or 'Important publications in biochemistry').

Since Wikipedia is a community project, anyone can sign up to be an editor. Perhaps some physiologists out there might fancy a go? Apart from the 'physiology' page, other options for editing might be entries on famous physiologists, or on your scientific area. These latter may well be where your students get a lot of their information (!), so it would be better if they were accurate.

Pig ignorant

When I was at the Institute of Animal Physiology, papers had to be seen by the Director before submission to a journal (a process that still continues at what is now The Babraham Institute). This was usually a formality so long as the manuscript had been read by a 'colleague'. I'm glad to say that I was not the colleague who'd been involved with the paper that, having been through this internal process, and subsequently reviewed, accepted and copyedited, was at the page-proof stage before anyone noticed it read 'The pig, like other ruminants. . .' .

Ann Silver

Heart disease link to oxygen in the womb

Studies of chick embryos and babies in La Paz, the highest city in the world, are helping to uncover a link between low oxygen in the womb with fetal growth restriction and heart disease in later life

Prenatal origins of heart disease

Heart disease is the greatest killer in the UK today, imposing a substantial burden on the nation's health and wealth. The concept that traditional risk factors, such as smoking and obesity, increase the risk of heart disease is familiar to all of us. However, it does little to explain why some individuals develop the disease and others do not. Hence, in addition to the genetic basis of cardio-vascular disease, a third concept has now become established – one of developmental programming. This states that a component of both the cardiovascular health we enjoy and the risk of heart disease in adult life can be predetermined before birth, not only by our genes but also by their interaction with quality of the prenatal environment. In pregnancy complicated with adverse intra-uterine conditions, physiological adaptations are enforced in the unborn child and placenta, which can reduce the growth of the fetus[1] and alter the development of key organs and systems, such as the heart and circulation. Whilst they are necessary to maintain viable pregnancy and sustain life before birth, these adaptations come at a cost, claiming many biological trade-offs. Overwhelming evidence in humans in more than a dozen countries now links development under sub-optimal intrauterine conditions leading to low birth weight with increased rates of heart disease and its major risk factors – hypertension, atherosclerosis and diabetes (Barker, 1998).

During pregnancy, the quality of the environment in the womb is largely determined by the available nutrient and oxygen supply to the growing young. As such, the association between poor conditions *in utero* and increased risk of heart disease in adulthood has, literally, exploded a new field of research investigating the effects of changes in nutrition during pregnancy on programming

Dino Giussani.

cardiovascular disease (McMillen & Robinson, 2005). However, in contrast to the international research effort, the contribution of reductions in oxygen delivery to the fetus, of the type that can occur during pre-eclampsia or placental insufficiency, to reductions in fetal growth and the developmental programming of cardiovascular disease remains very much under-studied. To address this, the group's programmes of research has recently adopted a two-prong approach addressing questions in a specific human population and determining mechanisms in specific animal models.

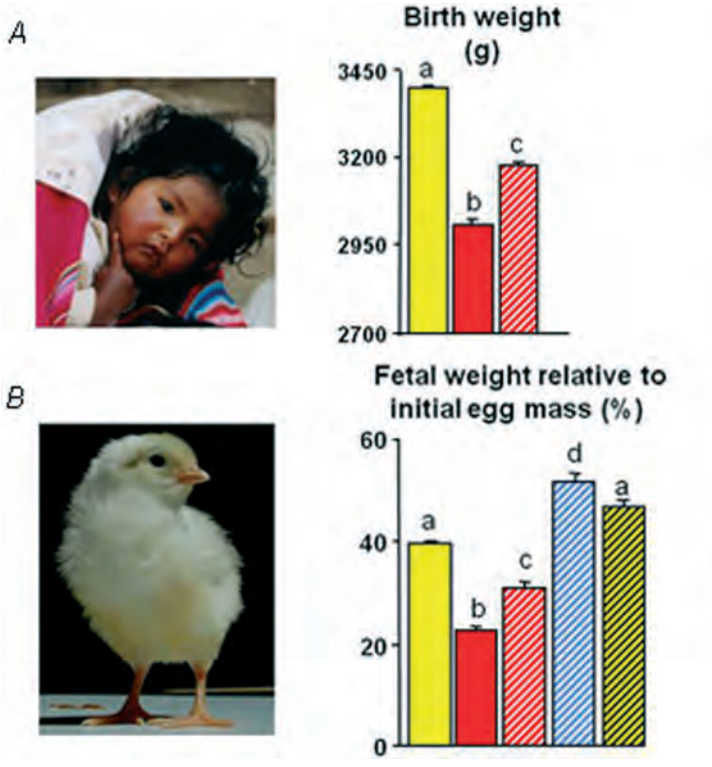

Figure 1. Effect of development at high altitude on human birth weight (*A*) and on the weight of the chick embryo at the end of incubation (*B*)

Values are means + S.E.M. SLSL, sea level embryos incubated at sea level; SLHA, sea level embryos incubated at high altitude; HAHA, high altitude embryos incubated at high altitude; HASL high altitude embryos incubated at sea level; $SLHAO_2$, sea level embryos incubated at high altitude with oxygen supplementation. Different letters are significantly different by one-way ANOVA with Student–Newman–Keuls or Dunn's tests, as appropriate ($P < 0.05$).

Pregnancy in the Andes

The greater the altitude, the lower the partial pressure of oxygen in the atmosphere. Hence, pregnancy at high altitude is an experiment of nature that permits investigation of the effects of poor oxygenation on fetal development. Epidemiological studies of human populations were carried out in Bolivia (Giussani *et al*. 2001), as this country is geographically and socio-economically unique. Bolivia lies in the heart of South America and it is split by the Andean cordillera into areas of very high altitude to the west of the country (4000 m) and sea level areas as the east of the country spans into the Brazilian Amazon. Facilitating the study design, the two largest cities, and therefore the most populated with approximately 2 million inhabitants each, are La Paz (4000 m) and Santa Cruz (400 m). Bolivia is also socio-economically unique as both La Paz and Santa Cruz are made up of striking economically-divergent populations. In developing countries, especially in Bolivia, there is an unsurprising strong relationship between socio-economic and nutritional status. Therefore, it was of interest to determine whether the known reduced fetal growth that occurs in the high-altitude regions of Bolivia was primarily due to lack of oxygen in the womb or due to the maternal socio-economic nutritional status. Birth weight records were obtained from healthy term pregnancies in La Paz and Santa Cruz, especially from obstetric hospitals and clinics selectively attended by wealthy or impoverished mothers. Analysis revealed a pronounced reduction in birth weight in babies from high altitude compared with low altitude, despite similarly high maternal economic status (Fig. 1*A*). Babies born from poor mothers at sea level also showed a reduction in birth weight; however, the effect of poverty was not as pronounced as the effect of high altitude on birth weight. Interestingly, babies born from highland as well as impoverished mothers did not have the greatest reduction in birth weight, as one would have expected. Rather, counter-intuitively, these babies were actually heavier than highland babies born from families with a high socio-economic status! The apparent conundrum was easily explained by assessing the ancestry of the families. The low socio-economic group of La Paz contained a high percentage (92%) of women from Amerindian origin with Aymara indian paternal and maternal surnames. In contrast, the high socio-economic group of La Paz contained a high European admixture. These findings, therefore, revealed not only that fetal oxygenation relative to fetal nutrition was an important determinant of fetal growth, but also that prolonged high altitude residence ancestry conferred protection against this effect. Reduced fetal growth at altitude is correlated with the duration of high altitude residence, independent of maternal nutrition: the longest resident population experiencing the least decline and the shortest residence groups demonstrating the most reduction in birth weight (Fig. 1*A*). Accordingly, reductions in birth weight at elevations greater than 3000 m above sea level are greatest in Colorado, intermediate in Andeans and least in Tibetans (Moore, 1990).

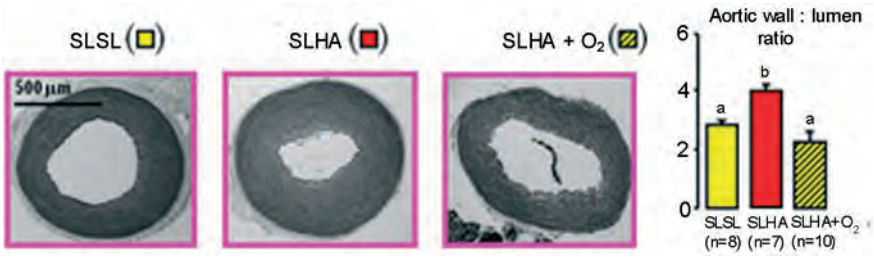

Figure 2. Fetal aortic thickening at high altitude

Photomicrographs of representative examples of aortic sections and the mean + S.E.M. of the aortic wall-to-lumen area ratio for sea level chick embryos incubated either at sea level (SLSL) or high altitude (SLHA) and in sea level chick embryos incubated at high altitude with oxygen supplementation (SLHA + O_2). Different letters are significantly different by one-way ANOVA with Student–Newman–Keuls test ($P < 0.05$).

Mountain chicks hatch clue to fetal development

The second prong of our approach exploited the chick embryo as an animal model. In contrast to all mammals (bar monotremes), in avian species the effects on the fetus of lack of oxygen can be studied directly, without additional effects of hypoxia on the mother and the placenta, and without the

Native Bolivian children at the Sun Island on Lake Titicaca, La Paz (3827 metres above sea level). Photos by Kristin Giussani.

Native Bolivian mother and child at the Tarabuco Saturday market, between Sucre and Potosi (4090 metres above sea level).

confounding problems of poverty and ethnicity in highland human populations. A recent study published in *The Journal of Physiology* (Giussani *et al*. 2007) reasoned that if oxygen alone had a real role in the direct control of fetal growth and a developmental origin of heart disease, then fertilised eggs from hens native to sea level should show growth restriction and an increased risk of heart disease when incubated at high altitude. In addition, the experiment could be done the other way around, something almost impossible to test in human populations. Hence, fertilised eggs from hens native to high altitude could be incubated at sea level to determine if the fetus recovers its growth and the risk of heart disease is normalised. Again, the study was done in Bolivia. The data show that incubation of sea level embryos at high altitude led to a 50% growth restriction, but incubation at high altitude of embryos from hens native to high altitude only led to 30% growth restriction (Fig. 1*B*). Furthermore, incubation at sea level of embryos from hens native to high altitude not only restored growth, but these embryos were actually larger than sea level embryos incubated at sea level. Interestingly, incubations at high altitude, irrespective of highland ancestry, led to an increase in the thickness of the walls of the fetal heart and of the fetal aorta – early markers of cardiovascular disease. Reassuringly, these effects of high altitude development on cardiovascular remodelling could be prevented by incubation at sea level or by incubation at altitude with oxygen supplementation (Fig. 2).

Vitamin C and health interests grow: bringing the Andes to Cambridge

The group's latest programmes of research have established that the adverse effects of prenatal hypoxia on cardiovascular development may be secondary to the generation of oxidative stress. If true, this is an exciting possibility to combat the developmental programming of heart disease as it offers the potential for treatment with antioxidants of pregnancies complicated with reduced oxygen delivery to the fetus, be it at sea level, such as during pre-eclampsia or placental insufficiency, or during pregnancy at high altitude. The latest data show that exposure of pregnant rats to reduced oxygenation at normal barometric pressure here in Cambridge does not affect maternal food intake but it yields offspring with cardiovascular problems both at the end of gestation and in adulthood. Importantly, these effects of hypoxic pregnancy can be prevented by giving the mothers antioxidants in the drinking water. This latest work not only highlights that fetal oxygenation independent of nutritional and genetic risk factors is a potent trigger for a prenatal origin of heart disease, but the antioxidant findings provide science a unique and timely opportunity to bring 'preventative medicine back into the womb.'

[1]Fetus. Much controversy exists over the spelling of the word 'fetus'. *The Oxford Dictionary* states that the word was adopted from the Latin noun meaning 'offspring' and the verb 'feteo' meaning 'to breed'. Interestingly, the Latin verb 'foeteo' means 'to have an offensive smell'. The spelling 'foetus' is therefore not merely incorrect, but might be regarded as being gratuitously unkind to the healthy fetus (From *Reproduction and the Fetus*, ALR Findlay, Edward Arnold, 1984.)

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Group sponsored by The British Heart Foundation, the BBSRC, The Lister Institute for Preventive Medicine, The Royal Society and The Wellcome Trust. Dino Giussani is a member of the Cambridge Centre for Trophoblast Research.

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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 photos. Contact Linda Rimmer (lrimmer@physoc.org) with your suggestions.

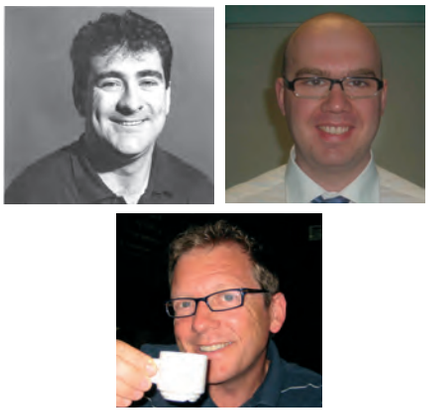
Vascular adaptations and exercise training: how to convince your cardiologist that physiology is important

A physiologist who works with cardiologists sometimes needs a thick skin. I vividly recall the first talk I gave, as an enthusiastic PhD student, to a room full of busy interventional cardiologists. After 30 minutes proselytizing the 'undoubted benefits of exercise and cardiac rehabilitation', the Professor of Cardiology stood up and solemnly stated 'Everyone knows that one is born with a certain number of heart beats, and the more you exercise the quicker they get used up'. I was left to consider whether the Professor, my PhD supervisor, was entirely committed to our planned exercise training studies!

During the more recent era of cardiovascular (CV) 'block-buster' drugs, any suggestion that exercise may be important in primary or secondary prevention of cardiovascular disease was likely to be met with the assertion that 'Cardiac rehabilitation should consist of making sure patients are compliant with their drug regimes'. To a GP or a Specialist who has been educated, overtly or otherwise, through an era of emphasis on drugs for CV risk factor modification, it is logical that an intervention such as exercise, which has relatively modest impacts on such risk factors, should have to justify itself. Of course this view is based on the notion that the effects of exercise training (or physical activity) are secondary in nature: that is, exercise exerts its benefits by modifying well-established risk factors like blood pressure or lipid levels.

It is true that the effects of exercise on traditional risk factors are, on average, relatively modest compared to the direct impact of drug treatments (Thompson *et al*. 2003; Green *et al*. 2008*a*). Even if exercise is a 'poly-pill' and the benefits on each risk factor summate, they probably do not approach the combined impact of drug treatment with agents like statins and angiotensin converting enzyme inhibitors. Nonetheless, primary and secondary prevention analyses suggest that exercise (or cardio-pulmonary fitness) is associated with around 30% CV risk reduction, relative to inactivity or 'usual (!)' care (Green *et al*. 2008*a*). In secondary prevention (cardiac rehabilitation) studies, this benefit is additional to that associated with optimal contemporary medical and interventional management (Taylor *et al*. 2004). Clearly exercise decreases CV risk. But how?

One lead was provided by a recent analysis (Mora *et al*. 2007) which reported that changes in established and novel risk factors explained only about 50% of the cardiovascular risk reduction associated with exercise. That is, around half of the risk reduction associated with exercise is unaccounted for and cannot be explained by 'secondary' impacts of exercise on establish risk factors (Fig. 1).



Danny Green, Mark Black and Tim Cable (from top left, clockwise).

Perhaps it's time to consider direct impacts of exercise on the vasculature?

Exercise is associated with changes in both vascular function and structure. For example, it is well established that training programs enhance endothelial function (Hambrecht *et al*. 2003), although the type of exercise or the patient groups involved may influence the magnitude or indeed presence of any benefit. Generally, beneficial effects of exercise training have been observed in resistance and conduit arteries of both skeletal and coronary vascular beds in patients with risk factors or CV diseases, in whom vascular function may be impaired *a priori*. Benefits in younger or healthier subjects have been less universally observed. Changes in arterial size, or arterial remodelling, also occur with exercise training and may also be endothelium dependent (Green *et al*. 2004).

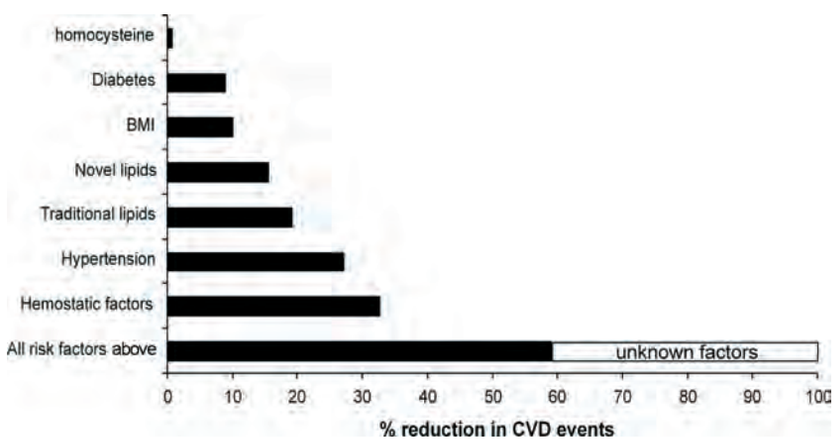


Figure 1. Percentage reduction in cardiovascular disease events associated with physical activity that is explained by risk factor modification (adapted from Mora *et al*. 2007)
Differences in risk factors explain ~50% of the relative cardiovascular risk reduction associated with exercise. This statistical modelling suggests that around half of the risk reduction associated with exercise cannot be explained by established or emerging risk factors.

Hence, although there is strong evidence in humans that exercise training has direct effects on vascular function and size, some inconsistencies exist in the literature and many questions remain. What is the stimulus responsible for training effects on the vasculature? Do the functional and structural changes interact or co-exist? Are adaptations equally apparent at all levels of the arterial tree?

What is the stimulus responsible for training effects on the vasculature? Repetitive exposure to increased shear stress may be a key physiological stimulus to vascular adaptation in humans. Acute exercise is associated with increased blood flow and driving pressure, but the blood flow (and shear) profile associated with exercise may depend upon the nature of the exercise itself and whether the vascular bed feeds active or inactive muscle (Fig. 2). Leg exercise, for example, induces changes in upper limb blood flow which include a substantial retrograde flow component (Green *et al*. 2005). In contrast, hand-grip exercise is associated with increased anterograde flows and shear, but modest change in retrograde flows. This difference in flow patterns may explain the observation that many exercise training studies involving

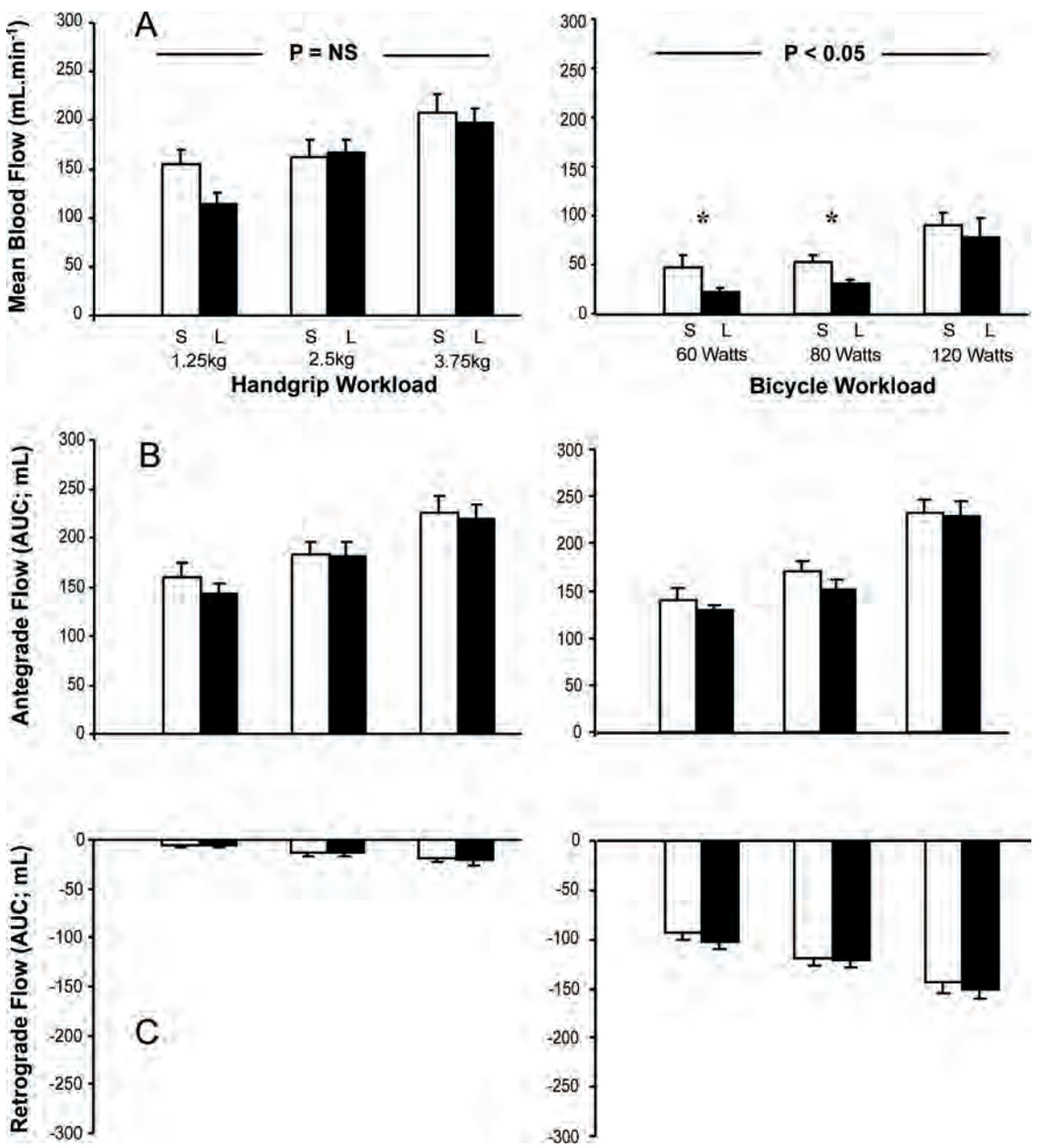


Figure 2. Effect of localised hand grip (left panels) and cycle ergometer (right panels) exercise on brachial artery haemodynamics

Mean blood flow (*A*), antegrade (*B*) and retrograde (*C*) flows during exercise under saline (S; open bars) and nitric oxide (NO) blockade conditions with L-NMMA (L; filled bars) infusion are displayed. L-NMMA significantly decreased flows under the cycle condition only. There is substantial retrograde flow during cycling which is not evident during hand grip exercise. Different forms of exercise have different effects on patterns of blood flow/shear stress and induce different NO contributions to flow. From Green *et al*. 2005. AUC, area under the curve.

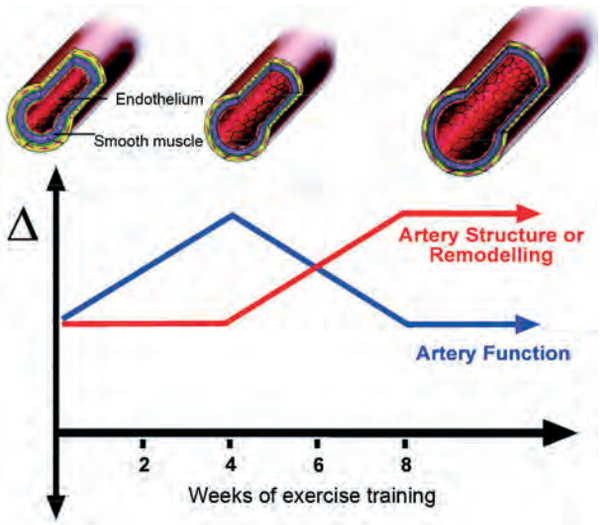


Figure 3. Changes in artery function and structure in response to exercise training in humans
Studies performed in both animals and humans suggest that rapid changes occur in artery function, including nitric oxide (NO) bioavailability, in response to exercise training, and that these changes may be superseded by arterial remodelling and subsequent normalisation of function.

localised handgrip training have not produced significant improvement in endothelial function, whilst studies which have utilised large muscle group exercise involving the lower limbs (cycling, running, etc), have often observed improvements in vasodilator function and/or capacity, even in the untrained upper limbs (Green *et al*. 2008*b*).

Do functional and structural changes interact or co-exist? Toni Tinken and Dick Thijssen recently investigated another explanation for the inconsistencies in exercise

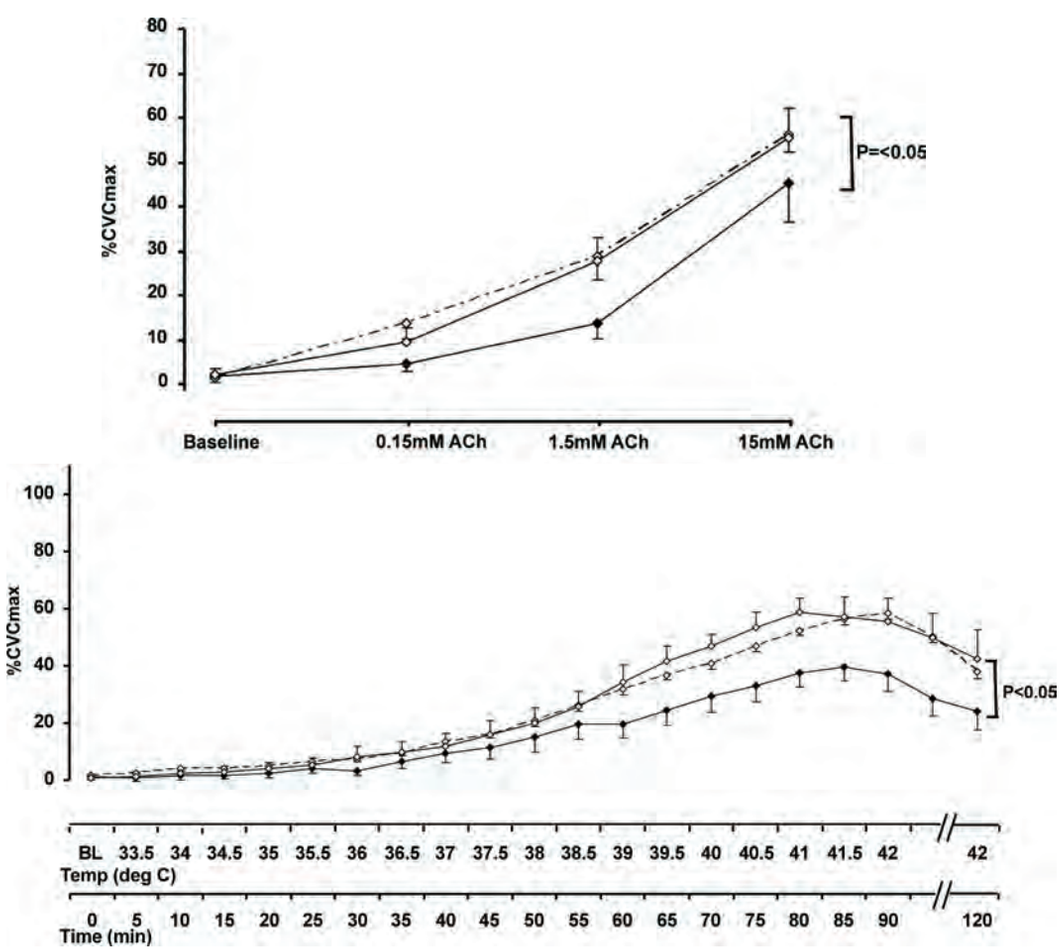


Figure 4. The impact of 12 (open diamonds, dashed lines) and 24 weeks (open diamonds, continuous line) of exercise training in older sedentary subjects, compared to data collected at entry to the study (filled diamonds, continuous line)
The contribution of NO to the ACh responses (top) and local heating (bottom) was significantly greater after training ($P < 0.05$). This abolished the initial difference that existed between the old sedentary and older fit subjects (Black *et al*. 2008). CVCmax, cutaneous vascular conductance.

training findings in humans, related to the time-course of change in function and structure (Tinken *et al*. 2008). In young men, conduit artery function improved during the early stages of exercise training, but then normalised as arterial outward remodelling occurred (Fig. 3). As originally suggested by Harold Laughlin and colleagues, it seems likely that early functional adaptations may be superseded by arterial remodelling, which enables function to normalise at the larger structural set-point. The lack of difference in function when assayed at later time points may also explain the disparity between studies in the literature regarding the impact of training, particularly in healthy younger subjects.

Are adaptations equally apparent at all levels of the arterial tree? In resistance arteries, improvements in vascular function and arterial remodelling may contribute to the hypotensive effect of training, apparent at rest, and also the increase in vascular conductance which absorbs large training-induced increases in cardiac output manifest during exercise. In conduit arteries, direct effects of exercise training on endothelial function may decrease macrovascular risk. A separate question relates to the possible impact of exercise training on microvascular function. Mark Black recently addressed this question in his PhD work by comparing healthy young subjects to exercise-trained and fit older subjects and also older sedentary controls (Black *et al*. 2008). The latter group were subsequently randomised to an exercise training or control group for a period of 24 weeks. The impact of localised heating and also acetylcholine infusion on skin vasodilator function was assessed. NO blockade was performed to characterise the contribution of this substance to microvascular changes observed. Sedentary ageing was associated with diminished NO-mediated vasodilator function in response to both heating and ACh administration, whilst exercise training in the older sedentary subjects reversed this (Fig. 4). Maintaining fitness as you age, or taking up exercise training, improves microvascular function. These findings provide a mechanistic rationale for the promotion of exercise for the prevention of microvascular disease in humans and may be important if the large increases in obesity and type 2 diabetes eventuate in the coming decades, as predicted.

Final word: If we are to optimise the design of interventions aimed at preventing cardiovascular disease/s, then it is important to understand the physiology which underpins vascular adaptations. Exercise is important, even for cardiologists. A study from Rainer Hambrecht's group (Hambrecht *et al*. 2004) compared the effects of optimal interventional management of coronary artery disease, including stenting, to exercise training alone. Both groups received comparable medical management. After 12 months, the 'stent' group exhibited markedly decreased stenosis diameter (81% to 2%), whereas the exercise training group, who did not have an angioplasty or a stent, exhibited no change in lesion size (78% to 77%). Nonetheless, significantly higher event-free survival occurred with exercise training (88% *vs* 70%). It seems that exercise exerts beneficial effects on vascular function/remodelling and disease progression in the entire arterial bed, whereas stents apply a band-aid. The authors, a group of cardiologists, concluded that in contrast to exercise training, coronary interventions must be regarded as a palliative therapy with regard to the underlying process of atherosclerosis.

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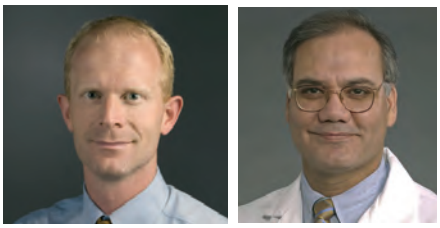
Negative consequences of physical inactivity on non-alcoholic fatty liver disease development

Leading a sedentary lifestyle is increasing the risk for development of non-alcoholic fatty liver disease (NAFLD) in westernized countries. Sudden cessation of physical activity appears to upregulate many processes known to initiate hepatic steatosis development

Sedentary lifestyle and poor dietary choices are increasing the risk for developing the metabolic syndrome and non-alcoholic fatty liver disease (NAFLD) in westernized societies. NAFLD encompasses a histological spectrum ranging from simple hepatic steatosis to non-alcoholic steatohepatitis (NASH), advanced fibrosis and cirrhosis. It is estimated that ~30% of the US adult population has excessive fat accumulation in liver, reaching levels as high as 75–100% in obese and morbidly obese individuals. NAFLD is considered the hepatic manifestation of the metabolic syndrome and is strongly associated with reductions in insulin sensitivity, increased rates of gluconeogenesis, impaired insulin response to suppress gluconeogenesis, and impaired fatty acid oxidation (reviewed by Rector *et al*. 2008*c*). Contributing to hepatic steatosis is: (1) excess dietary fat packaged as triglycerides (TG) in chylomicrons, (2) increased free fatty acid (FFA) flux from adipose tissue lipolysis, (3) increased *de novo* lipogenesis, (4) diminished exportation of TG into very low density lipoproteins, and (5) reduced hepatic fatty acid oxidation.

The present 'gold standard' management of NAFLD and NASH includes lifestyle modification targeted at increasing physical activity and reducing energy intake. Weight loss by energy restriction alone or in combination with exercise training has been shown to reduce hepatic fat content. In addition, exercise training in the absence of weight loss also improves hepatic insulin sensitivity by reducing endogenous glucose output (Shojaee-Moradie *et al*. 2007). Conversely, cross-sectional studies in humans have shown



Scott Rector (left) and Jamal Ibdah.

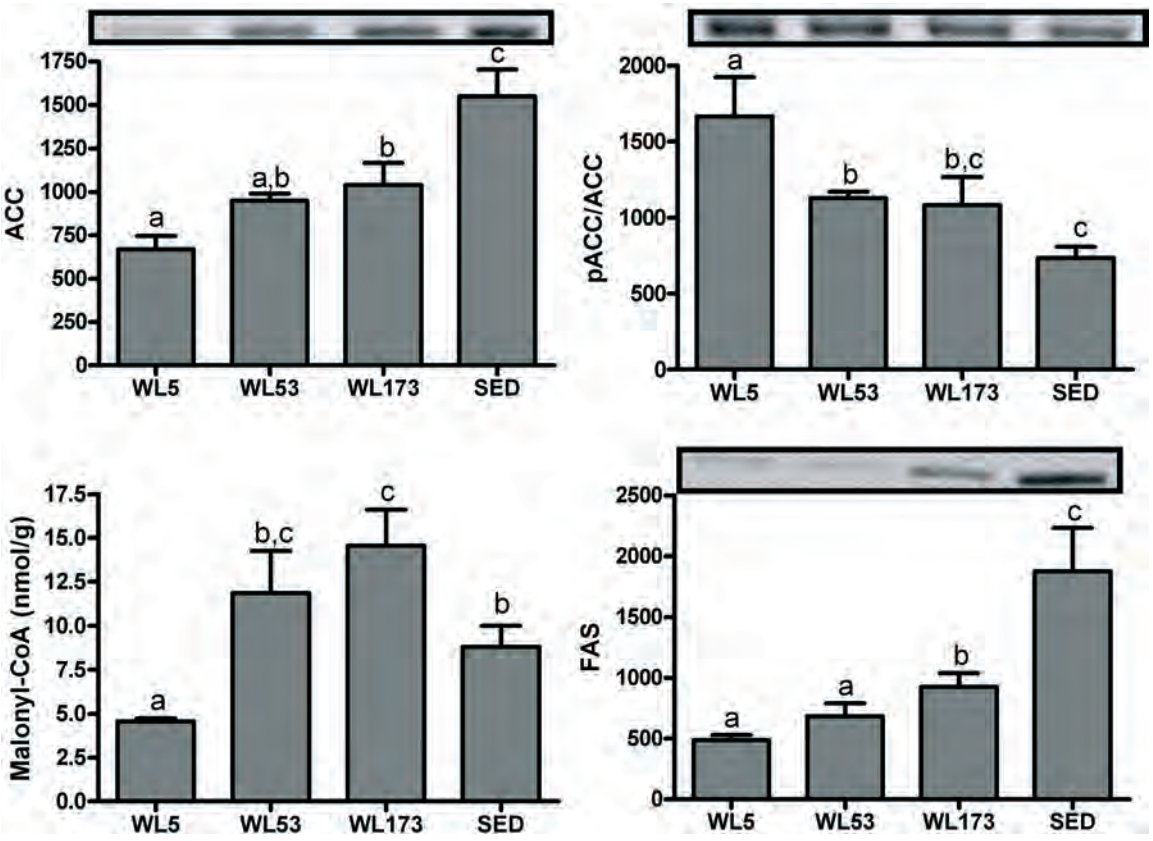


Figure 1. Effects of 5 h, 53 h and 173 h of physical inactivity on liver acetyl-coenzyme A carboxylase (ACC) (*A*), ACC phosphorylation (pACC) (*B*), malonyl-CoA (*C*) and fatty acid synthase (FAS) (*D*)

Values (means ± S.E.M.; n = 6-8) with different letters are significantly different (P<0.05).

that reduced habitual physical activity (Perseghin *et al*. 2007) is associated with NAFLD. In addition, less physically active individuals exhibit higher rates of hepatic FFA uptake compared with more active individuals (Hannukainen *et al*. 2007). More importantly, while the lack of regular exercise or physical inactivity is an 'actual' cause of death (Mokdad *et al*. 2004), the detrimental hepatic alterations that ensue following daily exercise cessation and undertaking a sedentary lifestyle are largely unknown.

We have utilized a commonly studied animal model of obesity and type 2 diabetes, the Otsuka Long–Evans Tokushima Fatty (OLETF) rat, to begin to address these questions. OLETF rats are hyperphagic, become obese and develop insulin resistance, type 2 diabetes, the metabolic syndrome, and NAFLD. However, when OLETF rats are given access to voluntary running wheel and allowed to exercise daily, body weight is suppressed (Rector *et al*. 2008*a*), whole-body insulin sensitivity is enhanced, and the development of type 2 diabetes is prevented (Shima *et al*. 1993). In addition, we have recently expanded these observations and reported that daily exercise also attenuates the development of hepatic steatosis in the OLETF rat in part by increasing hepatic fatty acid oxidation and reducing key *de novo* lipogenesis proteins (Rector *et al*. 2008*a*,*b*).

While mounting evidence suggests a negative impact of physical inactivity on the growing problem of NAFLD, little information exists to explain the reason for this occurrence. In order to gain novel mechanistic insight into initial detrimental effects of daily exercise cessation on hepatic lipid metabolism, OLETF rats that had been given access to voluntary running wheels had the wheels locked (wheel lock; WL) for 5 hours (WL5), 53 hours (WL53), or 173 hours (WL173) . To our knowledge, we are the first to report that the sudden cessation of daily exercise in a hyperphagic/obese model activates a subgroup of precursors and processes known to initiate hepatic steatosis (Rector *et al*. 2008*a*,*b*). In spite of no significant change in many peripheral factors previously associated with hepatic steatosis (body weight, fat pad mass, food intake, serum insulin), we found a rapid decline in complete fatty acid oxidation in liver and hepatic mitochondrial enzymes in the days after the cessation of daily exercise. In addition, cessation of daily exercise quickly increased the hepatic protein contents of fatty acid synthase (FAS) and acetyl-coenzyme A carboxylase (ACC), reduced ACC phosphorylation status (resulting in increased activation), and dramatically increased hepatic malonyl-CoA concentrations (Fig. 1), all integral steps in hepatic fatty acid synthesis. Despite the observed increase in malonyl-CoA (known to be associated with increased lipid deposition and reduced fatty acid oxidation) seen with exercise cessation, significant hepatic TG accumulation was not apparent with 173 hours of exercise cessation (Fig. 2) (Rector *et al*. 2008*a*). However, it is unlikely that the beneficial effects of daily physical activity on hepatic TG accumulation will persist indefinitely, particularly in a hyperphagic/obese model.

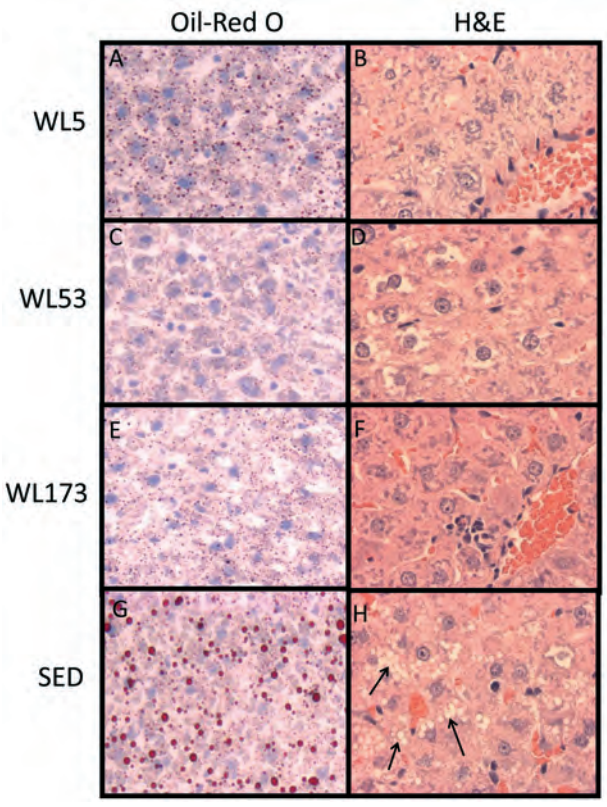


Figure 2. Representative images of haematoxylin and eosin (H&E) and Oil-Red O staining

Oil-Red O staining in WL5 (*A*), WL53 (*C*), WL173 (*E*), and SED (*G*). Red droplets indicate neutral lipid staining. H&E staining from WL5 (*B*), WL53 (*D*), WL173 (*F*) and SED (*H*). Note lipid vacuolization indicated by the black arrows.

These data strongly suggest that a sudden transition to a sedentary lifestyle increases susceptibility to NAFLD, and probably have important clinical significance as the OLETF rat model might be assimilated to hyperphagic/obese humans who continually stop and start exercise programs. Many populations have adopted increasingly intermittent physically inactive lifestyles at the same time that NAFLD is reaching epidemic proportions in the United States and westernized societies. Using exercise cessation as a tool may provide an opportunity to understand the time course of

molecular/biochemical events that lead to excessive hepatic fat accumulation, and thus future time course studies are warranted.

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Statistical methodology and reporting – the case for confidence intervals

Peter Cahusac.

Jack just finished collecting some more data on the effects of rhubarb extract #654 (RE654) on the membrane potential of spinal neurones. He passed the new data over to Olivia who had already started up the statistics package on her computer. So far the results hadn't quite reached statistical significance $P < 0.05$; adding the new data would hopefully change that – fingers crossed. Expectantly they both awaited the output of the t test. Yes! Significant! The P value was 0.033, that's good enough. They quickly entered this last bit of data analysis into their now overdue manuscript: '...RE654 also depolarised the resting membrane potential, from –64.7±2.0 to –57.6±1.9 mV ($P < 0.05$, $n = 20$)', and clicked the submit button to the online journal. Right, job done, off to the pub.

Despite the caricature, most people will identify with aspects of the above scenario. Some will also note statistical inadequacies. Recently I spent a couple of days reviewing the statistical methodology and reporting used by *The Journal of Physiology* research papers that appeared in the last four issues of 2008. Among other things I looked at what statistical tests were used, how results were reported, paying particular attention to whether confidence intervals were used. I also noted whether the standard deviation (S.D.) or standard error (S.E.) was preferred, and whether which was used was clearly stated.

As expected, the *t* test was the most popular test, being used in no fewer than 44 of the 60 papers. Last year, readers were treated to a fascinating history of this test (Brown, 2008). In doing a *t* test a statistical package typically churns out the means, each given with their standard error of the mean (S.E.M.) and S.D. Also given are the *t* value, sample size or degrees of freedom, and often the confidence interval. In reporting results, most research papers in my sample chose to give their calculated statistic (e.g. mean) ± some measure of variability. The large majority (46 of 58 papers which gave such measures) preferred to use the S.E., with only seven papers using exclusively the S.D. In most papers, which one was used was clearly stated in the Methods section. However, in six papers it was unclear or one had to look in figure or table legends to find which was used. In a further five papers (9%) there was no mention of what measure of variability was used. One of these was an Open Access paper which gave 57 summary statistics using ± yet nowhere indicated what measure of variability (S.E. or S.D.) was used. My survey results for *The Journal of Physiology* were similar to those for another study which examined 88 research papers in the medical journal *Infection and Immunity* (Olsen, 2003). There, 12 (14%) failed to identify the measure of variability. Why the sloppy reporting? Part of the reason may be that the difference between the S.E. and S.D. is not fully understood by researchers, and that these terms may be used interchangeably (Altman & Bland, 2005). Both S.D. and S.E. are measures of variability, and are related. The S.D. is an estimate of the variability of data points within a population, based upon a sample drawn from that population. In contrast, the S.E. is an estimate of the variability of a sample statistic (such as the mean) obtained by sampling from a population. Hence, the S.E. is also a standard deviation – but of the sampling distribution. The fact that the S.D. and S.E. are both standard deviations (but of different things) and are related, no doubt causes confusion. The persistence of the ± sign in papers is sometimes merely due to it being demanded by journal editors and reviewers. However, many journals, including the *British Medical Journal*, no longer allow the use of the ± sign, and request

		Effect size	
		Large	Small
Statistical significance	Small *P* value < 0.05	No problem	Mistaking statistical significance for scientific importance
	Large *P* value > 0.05	Failure to detect a scientifically important effect	No problem

Table 1. Using *P* values can be misleading when there is a small effect size and small *P* value, and when there is a large effect size and a large *P* value. Adapted from Rosenthal *et al*. (2000).

authors to clearly state whether the S.E. or S.D. is quoted.

In my survey I looked at how *P* values were reported. Giving the actual *P* values obtained by statistical tests is useful in that it indicates how significant the result is. Giving $P = 0.048$ or $P = 0.052$ indicates marginally significant and marginally non-significant results, respectively. Giving $P = 0.002$ and $P = 0.65$ indicates highly statistically and clearly non-statistically significant results. Usually extremely small *P* values can be expressed as $P < 0.001$, even though a computer output gives 0.000. Communicating information via the *P* value was something that the statistician and biologist R. A. Fisher encouraged as "...in doing this we have a genuine measure of the confidence with which any particular opinion may be held, in view of our particular data" (Fisher, 1955)[1]. If values are reported merely qualitatively as $P < 0.05$ or $P > 0.05$, then quantitative information from the *P* value is lost. Unfortunately, such reporting is common practice in *The Journal of Physiology*.

I was keen to determine how many papers reported 95% confidence intervals. Only 3 of the relevant 58 papers did so. Incidentally, one paper (not one of the 3) stated in its Methods section: "Significance was defined by a *P*-value less than 0.05 (95% confidence)." That "95% confidence" was not what I was looking for, and further implies a misunderstanding of what a *P* value represents (but more on that in a moment). So what's the fuss? Readers will justifiably wonder how a confidence interval can materially add to a reported mean, its standard error, sample size and *P* value. Where to begin? Well, the procedure of null hypothesis significance testing (NHST), which is how we normally decide whether an intervention has had an effect or not, is undeniably useful and prevents us from over-interpreting results. However, it has attracted a steady stream of criticism over the years (Cohen, 1994; Sterne & Smith, 2001), including comments from some very distinguished quarters (Cox, 1982). A couple of contributions to this literature make entertaining reading, particularly (Salsburg, 1985) 'The Religion of Statistics as Practiced in Medical Journals'. Another (Gigerenzer, 1993) (in jest) reduces statistical testing to a Freudian ritual. The *P* value that we obtain in a statistical test is the probability of obtaining data as extreme, or more extreme as our sample, assuming a true null hypothesis (typically this is that there is no effect). Although often misunderstood, even by leading textbooks (Bland & Altman, 1988), this *P* value is not the probability of the null hypothesis being true. Nor can we claim, should we for example obtain a statistically significant difference in means ($P < 0.05$), that there is a 95% chance that there is a difference between these means (or the '95% confidence' stated above). Such claims commit the so-called inverse probability error (Fisher, 1947; Cohen, 1994), attributing a Bayesian-like probability to whether hypotheses are true or not (NHST only gives us *P*(Data|Hypothesis), while Bayes' theorem gives *P*(Hypothesis|Data)). One difficulty is that the null hypothesis is rarely true anyway (Chew, 1977; Cohen, 1994). If you get enough data then you will almost always obtain a statistically significant result ($P < 0.05$ or $P < 0.01$ etc) – but the size of the effect may be extremely small and inconsequential, of little scientific interest. The statistical significance which we obtain from a NHST is routinely confused with the scientific importance and even the magnitude of the effect (size of the effect or effect size[2]). Often, in the Discussion section of a paper, much is made of the star-studded Results section (figures and tables emblazoned with *, **, ***). Then, sometimes it's difficult to publish without a '$P < 0.05$' appearing somewhere in the manuscript. However, relying on P values alone can be misleading, as can be seen in Table 1. If the size of the effect is so small as to be unimportant scientifically then its association with statistical significance (even $P < 0.001$) does not necessarily mean that the result is scientifically important. For example, not a week goes by without epidemiologists informing the public (exacerbated by media reporting (Blastland & Dilnot, 2008)) that a dietary component is statistically associated with either benefit or harm – typically such studies involve 1000's of participants, and we are rarely properly informed about the size of the effect. Conversely, when there is a large effect which fails to reach statistical significance, this is often reported as unimportant (Altman & Bland, 1995), and yet it may be very clear from a confidence interval that not enough data were collected.

[1]Fisher's paper is also of interest because it contains a polemic against the works of J. Neyman and E.S. Pearson who suggested the use of a fixed significance level of 0.05. Their proposals for Type II errors and confidence intervals were also attacked – but both these ideas are now accepted by mainstream statisticians.

[2]There is a distinction between these terms. The *size of effect* is given in the original units of measure (e.g. mmHg) and may be, for example, a mean difference. The *effect size* is a dimensionless but standardized quantity, examples being Cohen's *d* (the mean difference divided by σ), a correlation, or an odds ratio (Rosenthal *et al*. 2000).

How can one see this from a confidence interval? As an example, consider the effects of four different interventions on the blood pressure of patients with hypertension, where the horizontal axis represents the mean difference from pre-intervention (see Fig. 1). We assume (for the sake of argument) that any intervention that reduces blood pressure by 5 mmHg or more is worthwhile and clinically (or scientifically) important. In Fig. 1, 95% confidence intervals are plotted for each intervention. In each case, such an interval calculated from sample data will 95% of the time (in the long run) contain the population mean difference value for that intervention. Values bracketed within the interval are consistent with the sample mean difference, while those outside are not ($P < 0.05$). For interventions A and B, the midpoint (sample mean difference) in each interval is 6 S.E.s away from 0 mmHg, and they therefore have identical *t* and *P* values, and are clearly statistically significant (since these confidence intervals do not contain 0 mmHg). Intervention A, though statistically significant, is of little clinical (scientific) interest as its confidence interval lies close to 0, and does not contain or is not less than –5 mmHg. Intervention B is of much more interest as the confidence interval spans a range of values much lower than –5 mmHg (approx. –18 to –9 mmHg). For interventions C and D, the midpoint of each interval is situated only 1 S.E. away from 0, which gives them identical *t* and *P* values. Moreover their intervals span 0, so neither is statistically significant (i.e. each is $P > 0.05$). The interval in C does not include clinically important values (below –5 mmHg), and therefore should be of little further interest. The interval is narrow enough to indicate that we have collected enough data. In contrast, intervention D has a very wide interval that almost reaches to –14 mmHg. So although intervention D is not statistically significant (just as C) it is of much more interest, and indicates that we have not collected enough data. In the circumstances it would be premature to exclude D as a useful intervention. This result could represent that indicated at the bottom left cell in Table 1 (large *P* value and large effect size).

Typically, the 95% confidence interval is reported but others, including 90% and 99% intervals, are also used. Confidence intervals immediately indicate (i) statistical significance (Fig. 1*A* and *B* statistically significant), (ii) the size of the effect (B > D > A > C), (iii) the sensitivity of the study (A, B and C have enough power, D does not), (iv) the precision of the statistic (A and C have greater precision, their intervals are narrower, than B and D respectively). Providing the *P* value only gives us (i). Providing the mean ± S.E. gives us very limited information about (ii)–(iv). Although very rough 95% confidence intervals for mean differences may be mentally calculated quite quickly by the average reader of *The Journal of Physiology*, the same confidence interval calculations will probably not be so easy for other (e.g. non-parametric) statistics. It should be noted that the ± S.E. values given in the opening paragraph '...–64.7±2.0 to −57.6±1.9 mV...' cannot be used to calculate the confidence interval for the difference in means – which is what we are really interested in and to which the *P* value refers (this style of reporting individual means ± S.E. is common in *The Journal of Physiology* papers).

Let us return again to our opening scenario featuring Jack and Olivia, where Jack has just collected some more data. Strictly speaking, if they have already tested their data for an effect using a significance level of 0.05 and it fails to reach significance then that's it – however much more data they collect it is not possible to perform another significance test and claim a statistically significant effect (even if subsequently they obtain $P < 0.000001$). This is an issue about multiple testing and stopping rules. If Jack and Olivia had decided before collecting any data that they would periodically test for statistical significance, that would be fine, but they would need to adjust their significance level accordingly, for example using Bonferroni. So, if they had actually decided to test twice after collecting sets of data (as they actually did), then they would need to use 0.05/2 = 0.025 as their significance level, which with their *P* value of 0.033 would mean that they still could not claim a statistically significant result. It is a fact that, even if the null hypothesis is completely true, you are guaranteed to obtain a statistically significant result, at whatever level you choose,

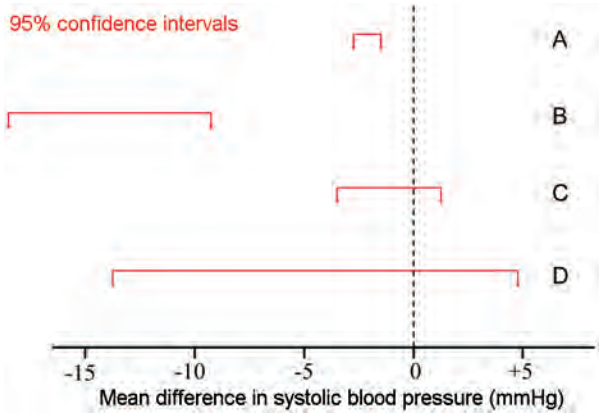

Figure 1. The results of 4 different interventions A – D on the blood pressure of patients with hypertension

The results from each intervention are plotted as 95% confidence intervals along the horizontal axis, in mmHg. For interventions A and B the midpoint (sample mean difference) in each interval is 6 S.E.s away from the 0 mmHg difference, and therefore have identical *t* and *P* values, and clearly statistically significant (actually $P < 0.001$). For interventions C and D, the midpoint of each interval is situated only 1 S.E. away from 0 mmHg, which gives them identical t and *P* values. Adapted from Reichardt & Gollob (1997).

if you continue to add more data to existing data and repeatedly test for significance. Problems like this have prompted some to use the Likelihood approach (Edwards, 1992; Royall, 2004).

Actually, confidence intervals can help us out here too. Continuing with the example illustrated in Fig. 1, and values given in mmHg. If we have collected some data and the 95% confidence interval for the difference in means includes both 0 and –5, then we know immediately that the study was not sensitive enough (i.e. power was too low, as seen in D). The S.E. is too large. Typically this can be reduced by increasing the sample size, that shrinks the confidence interval, until it is acceptably small. How small? Well, a nice stopping rule is suggested by Armitage *et al.* (2002) (p. 615). We should continue collecting data until our 95% confidence interval is just less than 5 units wide. In this way, if the interval includes 0 then it will exclude –5, and if it includes –5 then it will exclude 0. (If it just happens to fall in between 0 and –5 then we would claim a statistically significant effect but it would not be scientifically important.) Note that we are using the width of the confidence interval, not the smallness of the *P* value, to decide whether we have enough data. This procedure can be elaborated. For example, if we were not interested in interventions that reduce blood pressure by up to 4 mmHg, but were interested in interventions that reduce pressure by at least 10 mmHg, then we could continue collecting data until our 95% confidence interval was just less than 6 units wide. Few researchers appear to be aware of this useful stopping rule that allows us to collect data until the required precision is obtained. It forces us to explicitly recognise a size of effect which we believe to be scientifically important, and has the surprising advantage that it does not fall foul of the loss of power due to multiple testing protocols (e.g. Bonferroni (Perneger, 1998)).

For some years now statisticians have been placing greater emphasis on reporting confidence intervals rather than just *P* values (Altman *et al*. 2000). Many medical journals (e.g. the *British Medical Journal*) insist on them – where appropriate. Only limited use is made of them in physiology, and the Instructions for Authors for *The Journal of Physiology* makes no mention of them. In a review of 370 papers published in journals under the auspices of the American Physiological Society in 1996, only two papers reported confidence intervals (Curran-Everett *et al*. 1998). This review, which appeared in the *Journal of Applied Physiology*, highlighted inadequacies of statistical reporting and made a strong case for using confidence intervals, rather than just null hypothesis testing. Ten years on, the December 2008 issue of the same journal finds little improvement, with just 4/35 papers reporting confidence intervals (a proportion similar to my 3/58 for *The Journal of Physiology*).

Why aren't confidence intervals used more widely? Perhaps they are considered superfluous to a results summary (as I used to think). Maybe they are just not understood, and there is a failure to realise what information they carry. Sometimes they can be embarrassingly wide! Whatever the reason, I hope that they will be better appreciated and appear more often in future issues of *The Journal of Physiology* and related journals.

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When motoneurons get ready: new insights into motor preparation

Advance information about forthcoming motor actions helps to prepare for rapid movement execution by triggering changes in neuronal activity a few hundreds of milliseconds before a movement is actually performed. These preparatory processes have been found to occur at many levels in the motor system, from the motor cortex to the spinal cord. We recently obtained evidence that even motoneurons, which are the most peripheral components in the spinal cord, respond in this way to advance information

From left to right, *front*: Annie Schmied and Christiane Rossi-Durand; *back*: Henri Burnet, Yann Duclos, Boris Burle.

The execution of an accurate voluntary movement requires the underlying motor command to be continually adjusted to match the changing demands of the behavioural context as quickly as possible. The motor system therefore has to assess the ongoing context and predict the various changes liable to occur in order to be ready to react immediately. The appropriate adjustment of the motor command to the requirements of the forthcoming motor task is mainly based on motor preparation.

Many studies on humans and other primates have focused on the central processes involved in motor preparation, using pre-cueing reaction time tasks. In these tasks, the voluntary command is triggered by a stimulus, the response signal (RS). Before the instruction to move is given by the RS, a warning signal (WS) provides the subject with advance information about the movement to be performed. It has been clearly established that prior information of this kind contributes to improving motor performances by shortening the time required to react to the RS, i.e. the reaction time (RT). In particular, when the WS provides information about the timing of the forthcoming RS, it

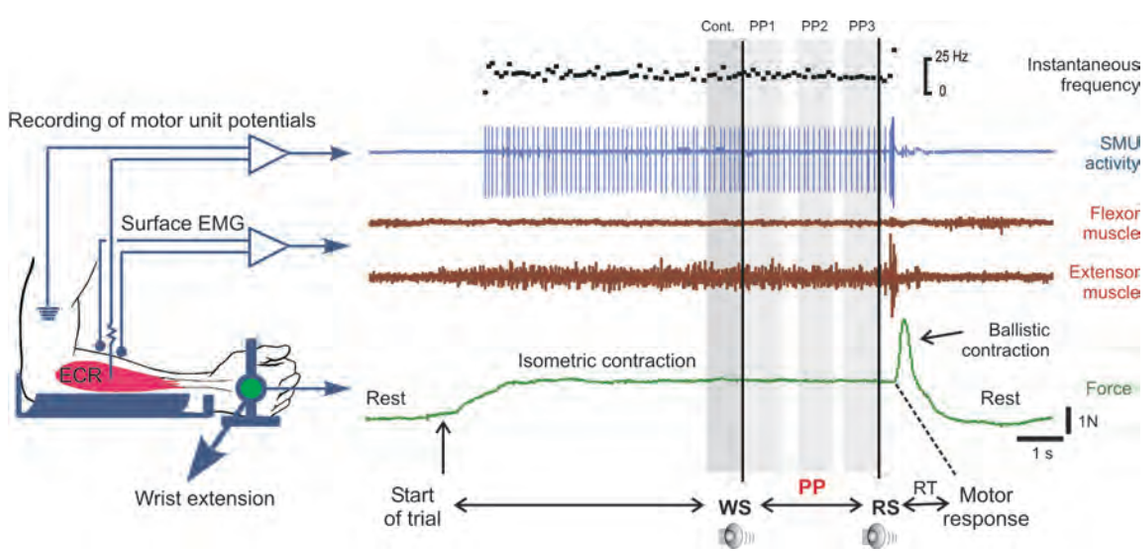

Figure 1. Experimental setup and pre-cueing RT motor task
To start a trial, the subjects had to selectively contract their wrist extensor muscles by pushing on the force transducer device with the back of their hand. They were asked to then maintain an isometric wrist extension (lower trace) at the force level required to recruit a single motor unit in the extensor carpi radialis (ECR) muscle. Single motor unit potentials were recorded using intramuscular tungsten microelectrodes. The motor unit activity (SMU activity) is also given by the instantaneous frequency curve around 12 Hz (top trace). When the force and the motor unit discharge rate stabilized, the two sounds used as cues were triggered successively (as indicated by the vertical black lines): the preparatory period (PP) began with the warning signal (WS) and ended with the response signal (RS). The duration of the PP was always 3 s. The trial ended with the motor response, i.e. a ballistic wrist extension performed as fast as possible after the RS. The reaction time (RT) was measured from the RS to the earliest detectable force change. The subjects returned to zero force level at the end of each trial. After a minimum rest period of 2 s, they launched the next trial at their own pace. To prevent the occurrence of premature or automatic motor responses, the RS was sometimes unpredictably replaced by a no-response signal. The motor unit discharge pattern was analysed during 4 periods of time within each trial, each including 9 motor unit potentials: the control period just prior to the WS (cont.; shown in dark grey) and three successive preparatory sub-periods preceding the RS (PP1, PP2 and PP3; in light grey). The mean force levels and surface EMG activities of the wrist extensor and flexor muscles were measured during these 4 periods.

helps the subject to be ready at the right time.

Single neuron recordings performed on awake monkeys trained to perform pre-cueing RT motor tasks showed that changes in the neural activity of many supraspinal motor structures occurred during the preparatory period (PP), which is the interval between the two signals (WS and RS). These changes therefore occur up to several hundreds of milliseconds before the onset of the response signal (see Riehle, 2005 for a review). There now exists evidence that preparatory processes are triggered at various levels in the motor system, including not only the primary motor cortex involved in shaping the motor command to be transmitted to the spinal motor networks, but also the spinal cord itself. Experiments using the Hoffman reflex and transcranial magnetic stimulation (TMS) on humans performing RT tasks have shown that changes in the excitability of spinal motor networks occur during the preparatory period in response to both central and peripheral afferent inputs (Bonnet *et al*. 1981; Touge *et al*. 1998; Hasbroucq *et al*. 1999). The idea that preparatory processes occur at the pre-motoneuronal level has been supported by data on awake monkeys showing the occurrence of changes in the firing rates of spinal interneurons, which were specifically associated with prior information about the movement parameters (see Fetz *et al*. 2002 for a review).

We recently addressed the question as to whether or not these changes in pre-motoneuronal activity occurring during motor preparation may also include motoneuronal activity (Duclos *et al*. 2008). For this purpose, the effects of motor preparation on motoneuron activity were studied in humans by combining single motor unit recording techniques with reaction-time methods. The pattern of human motoneuron activity can indeed be deduced from intra-muscular recordings of single motor unit activity, since there exists a one-to-one relationship between the action potentials generated by the motoneurons and the muscle fibres they innervate. The tonic activity of wrist extensor motor units

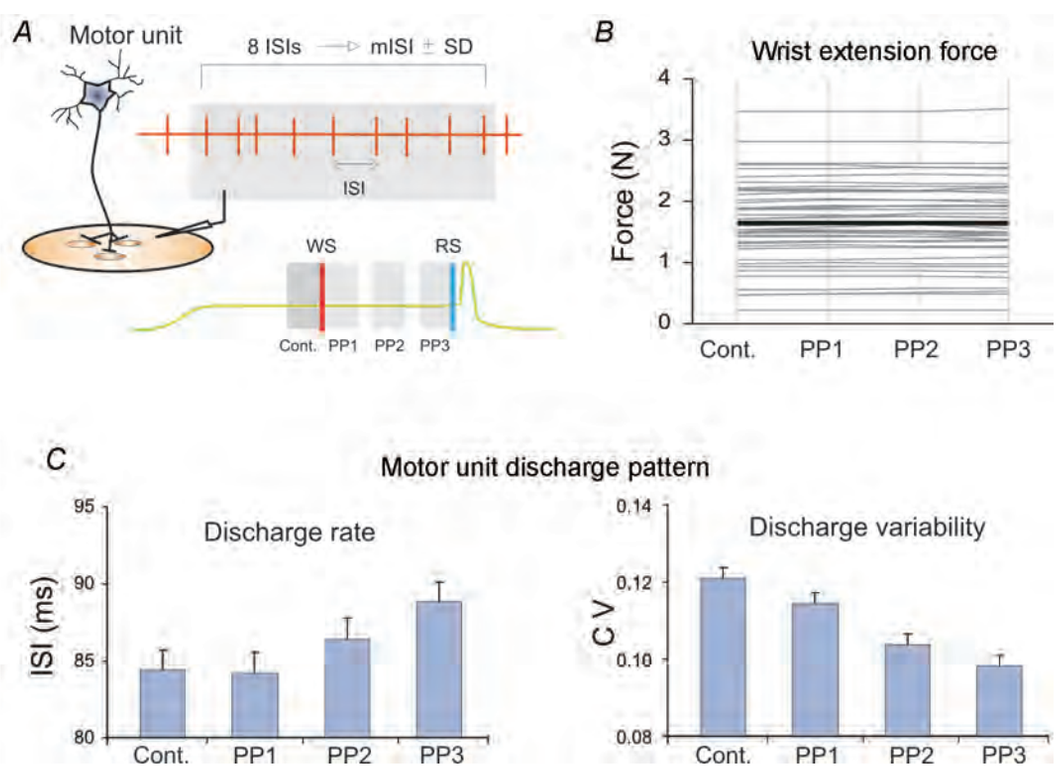

Figure 2. Effects of motor preparation on motor unit discharge patterns and force output

A, sketch of the motor unit activity analysis. The motor unit discharge pattern was characterized in terms of the means and standard deviations of the inter-spike intervals (mISI and SD) and by computing the coefficient of variation (CV = SD/mISI). The values were assessed from 8 consecutive ISIs analysed during different periods within each trial. The periods analysed (control, PP1, PP2, PP3) and the timing of the events are indicated in the lower diagram. With each SMU, the mean ISI, SD and CV values were obtained by averaging the values recorded in all the trials performed during the recording sequence. *B*, the mean force levels obtained during each of the 46 motor unit recording sequences (thin grey lines) and the median values obtained on the whole population tested (thick black line) did not differ between the control period and the three preparatory sub-periods. *C*, the bar graphs show the grand average of the mean inter-spike intervals and the coefficient of variation (mean + S.E.M.) obtained with the 46 single motor units tested during the control period and the three preparatory sub-periods. The ISI durations increased significantly and the CV values decreased significantly during the preparatory period. Both changes were found to occur gradually during the successive periods analysed ($P < 0.001$).

associated with voluntary isometric contractions was analysed during preparation for a ballistic wrist extensor muscle contraction, using a time preparation procedure in which the warning signal preceded the response signal by 3 s (Fig. 1). The changes observed in the motor unit tonic discharge pattern during the preparatory period show that the motoneurons are involved in motor preparation. The rate and the regularity of the motoneuron discharge patterns were consistently altered prior to the response signal and showed a slight lengthening of the mean inter-spike interval (ISI) and a marked decrease in the ISI variability (Fig. 2*C*). The lengthening of the inter-spike interval confirms that inhibitory mechanisms are activated during motor preparation. The finding that the slowing down of the motoneuron discharge rate during the preparatory period was concomitant with a decrease in the discharge variability was unexpected. It indicates that the integrative properties of motoneurons may be modulated during motor preparation, possibly as the result of spinal inhibitory mechanisms. These changes in motoneuron activity occurred gradually during the successive periods analysed and were most prominent at the end of the 3 s preparatory period. This time course suggests that the activation of these inhibitory mechanisms may be associated with the timing of the forthcoming response signal and may possibly serve to prevent premature motor output from occurring.

These data showing that the activity of motoneurons was modulated prior to the onset of a response signal provide evidence that anticipatory changes occur in motoneuron activity, just as they do in the neural activity of many supraspinal motor structures. This means that some central influences act on spinal motoneurons during preparation for action, i.e. well before it is time to act. The fact that no changes were detected in the force output during the preparatory period (Fig. 2*B*) confirms that the anticipatory changes in motoneuron activity were subtle enough to prevent any unwanted changes in muscle contraction from occurring prior to the instruction to move.

The finding that advance information may influence the state of the motor system, including even the most peripheral motor neurons in the spinal cord, supports the idea that motor preparation involves distributed processes, in line with the conclusion reached by Fetz's group (Prut *et al*. 2001 for a review).

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Noticeboard

The Journal of Physiology Symposia 2009

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

Non-Society 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

University College London, London, UK
14–16 June 2009
Bone Research Society/British Society for Matrix Biology Joint Meeting
www.bsmb.ac.uk/brs/

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 www.isanweb.org

Hilton Metropole, Brighton, UK
15–17 December 2009 BPS Winter Meeting 2009

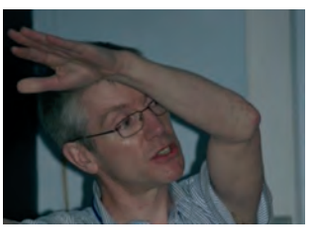
Cystic fibrosis (CF): better understanding, better lives

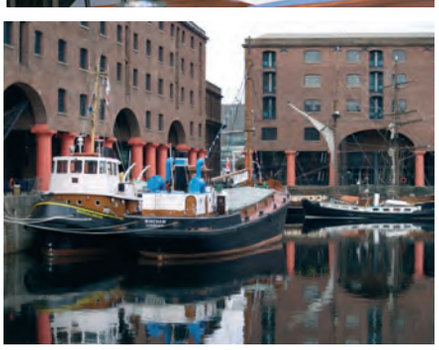
We followed up our successful event for external audiences on CF at The Royal Society in November 2007 (*Physiology News* **70**, 43), by holding it again at the BA Science Festival in Liverpool on the 9 September 2008, in partnership with the BSF, EuroCareCF and the Society for General Microbiology. The speakers were the same as for the original event, Ole Petersen, Alastair Innes, Mike Gray, David Sheppard and Vicky Cowell, but with one additional speaker, Eshwar Mahenthiralingam, from Cardiff University and the Society for General Microbiology. Esh talked about the problems caused by constant lung infections in CF patients.

About 70 people attended, including many members of the general public, clinicians, academics and other medical staff. Questions and debate at the end were excellent, with a lively audience and parents of CF children actively debating the issues with our speakers. One older man, whose grand-daughter (8 weeks old) had only recently been diagnosed with CF, talked in an animated fashion with our speakers and left the event with hope shining from his face. This made it feel very worthwhile!

The CF event also attracted media interest, with one of the speakers, David Sheppard, being asked to do a couple of radio interviews in Bristol (BBC Radio Bristol and Original 106.5 (Bristol)). Articles also appeared in the following: The Daily Telegraph; BBC News; Evening Standard (London); HealthJockey.com (India), Health Highlights (USA); Nuovo Farmaco Contro la Fibrosi Cistica, Bioblog, (Italy); Irish Health; Science Daily, Medicalnewstoday.com; Medicallexicon.com; and The Teheran Times. The BA Festival is a good place to attract media coverage.

Liz Bell





Engineering better health

The overall message from the Royal Academy of Engineering's conference on 19 November was a striking one – we can expect to have to know more and more about engineering in future to keep at the cutting edge of research in our areas of interest.

David Delpy (Chief Executive, Engineering and Physical Sciences Research Council), started proceedings by pointing out how much healthcare has already been revolutionised in the last 20 years, with innovations such as artificial joints and sophisticated imaging techniques now being taken almost for granted. However, an important issue is that some of the underpinning physics and engineering departments in universities, which produced the medical physicists and clinical engineers behind many of these innovations, have started to disappear. EPSRC will be funding three new biomedical engineering centres to try to address the shortfalls of previous years. EPSRC is also now well engaged in funding physiological flows and modelling, medical imaging, tissue engineering and cell therapy, ultrasound and translation research.

Peter Wells (Cardiff University) talked about advances in ultrasound imaging, including convergence with sophisticated software image fusion and synthesis to create easily understandable, medical textbook illustration-type images, for clinicians and surgeons. Gail ter Haar (Institute of Cancer Research) then discussed how ultrasound is being used to treat tumours. Ultrasound is a very flexible technology; at low power it is safe for medical imaging purposes, but at higher power, and with suitably focused beams, it is capable of killing tumours (with the advantage of no residual radiation effects when it is turned off). It is hoped that once rolled out, many lives of cancer patients will be saved. Sir Michael Brady (University of Oxford)

described other developments in medical imaging. We are now seeing the integration of different scanning techniques such as PET and CT into coherent systems able to integrate many types of data into one readout, showing what is happening in a spatial map of the body. This will have many applications, for example in monitoring the *in vivo* performance of drugs. The quantitative analysis of disease progression is becoming possible, but the field is being held back by the lack of people to do the research.

Brian Davies (Imperial College) discussed the evolution of robot and computer-assisted surgery, from the early days of robots adapted from other industrial uses, to the development of intelligent tools in surgeon's hands. The use of robots in the operating theatre has raised many interesting ethical and other issues, including safety for the surgeons and their patients, the question of who is responsible if an operation goes wrong (the surgeon, the company that sold them the robot?) and cost effectiveness. Hygiene and other issues mean that disposables for robot surgeons can be very expensive, but robotic surgery has been proven to deliver better, more precise surgical results, which is driving further innovation in the area.

Patrick Prendergast (Trinity College Dublin) spoke of how boundaries are being pushed in bio-engineering the musculo-skeletal system, with a move from bio-passive, to bio-active to bio-reactive devices through the development of intelligent bio-materials. There is a strong convergence between ICT and biological devices that may eventually lead to a new generation of bio-proactive devices. Degenerative diseases such as osteoporosis and arthritis are common, and may become repairable with bio-engineered implants such as total joint replacement, but also prosthetic devices interfacing with neuro-musculoskeletal sensory and actuation mechanisms. The future of engineering in this aspect of healthcare is being radically advanced from observing how bio-engineered systems interface with the body, separate systems and tissues, cells and, ultimately, the genome.

Lionel Tarassenko (University of Oxford) discussed a revolution underway in patient monitoring in and out of hospital. The WHO predicts an explosion of chronic diseases such as diabetes and asthma in the coming decades; the key to dealing with these will be to help patients actively manage their conditions. However, people struggle with this, resulting in many distressing, and expensive, hospital admissions. Technology is needed to assist self management, and this is now possible through the ubiquitous mobile 'phone. Software systems have been developed which allow patients to input data into their 'phones, which are then communicated to a hospital system under the supervision of a nurse. The system flags up problems as they emerge and facilitates two-way communication between patients and their medical carers. Trials have shown that this technology (see www.tplusmedical.com) promotes patient well being and reduces hospital admissions, and is gradually being implemented throughout the NHS.

Christofer Toumazou (Imperial College) extended this discussion to consider a possible paradigm shift leading towards the use of disposable healthcare devices integrated with mobile 'phone healthcare systems. The reality in the economics of providing effective healthcare is that demographics will result in an ageing population with fewer carers. This could drive a need for unobtrusive, low power body sensors, directly connected into hospital healthcare systems, with all the issues that raises in terms of providing secure systems.

David Williams (Loughborough University) talked about the potential of regenerative medicine to treat chronic diseases, including treating cells with growth factors and using stem cells. It is expected that such technologies will work very well in treating cardiovascular diseases. One issue is that, although some of the technologies being developed have been shown to work clinically, very little thought has been given to industrial production methods to yield efficient, automated manufacture. This needs to be addressed if such technologies are to be able to support health services for the general population.

Jon Cooper (University of Glasgow) rounded up the session with a taste of the advances we can expect. He thought that synthetic biology would initially have a bigger impact on biotechnology in the short term, and would then have a major impact on biomedicine. As devices become ever smaller, more will become possible in drug delivery, tissue engineering, microfluidics in diagnostics (lab on a chip), measurement of intracellular drug kinetics, and the ability to test how an individual patient's cells will respond to a particular treatment. Synthetic biology could even take us into sci fi-type dimensions, with the ability to design and manufacture biological-based devices and systems not existing in the natural world.

So I was left visualising a future where we find engineers hiding under every physiological lab bench, and where we advance into old age as increasingly sophisticated cyborgs linked into, and being continuously monitored by, hospital expert systems. And as for the artificial life-forms, I think my imagination is about to implode!

Liz Bell

Why does public health matter?

Rosalind Stanwell-Smith (London School of Hygiene and Tropical Medicine), kicked off the Parliamentary and Scientific Committee meeting on 9 December by reminding us of the long history

of public health initiatives going back to classical times. The School was founded in the days of the British Empire, when contact with a far-flung empire brought many problems with communicable diseases. The centuries have seen many shifts in perspective in public health issues. The infrastructure of ancient civilisations was aimed at protecting the comfortable lifestyles of the elite and limiting their contact with the great unwashed, but the 19th century saw a new generation of public health heroes, often medics concerned with sanitary issues, who highlighted the shocking conditions endured by the labouring poor, and campaigned tirelessly for proper water supplies, vaccination, etc.

However, politicians responded, even to overwhelming scientific evidence, only when they were personally inconvenienced. I particularly liked the example of the Great Stink episode in 1858 when Parliament only brought in much needed water supply/sewage legislation when the smell from the polluted River Thames reached their Parliamentary chambers. Wars also progressed public health and medicine, with policy makers unable to ignore the need for healthy servicemen. Active state intervention was vital in creating the public health infrastructures that we now take for granted. However, public perceptions of the appropriateness of this have started to shift, with some modern interventions on lifestyle issues such as smoking, alcohol dependency and obesity, being seen as symptomatic of a 'nanny state'. Public health legislation and policy has also evolved in a rather ad hoc way over time, often in response to individual crises – the last major overhaul of the legislation was in 1936 and is overdue for systematic review.

Lord Krebs (Nuffield Council on Bioethics, and former Chair of the Food Standards Agency) then introduced a recent Nuffield report on Public health: ethical issues. The report considered what the government, industry, other

organisations and individuals should do to lead a healthy life, using four case studies to illustrate the ethical issues: infectious disease; obesity; alcohol and smoking; and fluoridation of water. The report (available at www.nuffieldbioethics.org) discusses appropriate ethical and policy frameworks for such lifestyle health issues, attempting to balance the need to protect individual liberties against collective benefits for the community, and to look at when, and if, government should intervene, and why. A key concept coming out of this analysis was the role of a stewardship (rather than a 'nanny') state, which intervenes to reduce risks to others, protect vulnerable groups, educate and inform, and provide access to medical services. The overall aim should be try to ensure consent by incentives and avoid intrusion and coercion.

Smoking legislation is a good example of where broad public support has been obtained for legislation restricting the activities of individual smokers, where the risks of passive smoking can be seen as a threat to others, particularly children. Government has already shown signs of taking tougher action on alcohol, with the recent Queen's Speech highlighting the need to reduce misuse, and a 2007 WHO report advocating measures on pricing and restricting drinking in public. The debate on 24 hour licensing in the UK is heating up, with discussions on the impact on crime and spiralling NHS costs. Debates in the developed world thus show divergent views on the appropriateness of state intervention in the many diseases now driven by lifestyle choices. However, one thing that many people now recognise is that the business sector cannot always be relied upon to behave responsibly, a striking example being that of tobacco companies, now controlled in the developed world, but actively targeting developing countries instead.

Finally, Sir William Stewart (Chairman, Health Protection Agency) looked at the role of the Agency in public health. The Agency exists to protect the public from chemical, radiation and infectious disease hazards, and does not get involved in lifestyle disease issues. Its labs have been involved in investigating high profile cases such as the Litvinenko Polonium 210 poisoning incident, and accidents worldwide such as Three Mile Island. In medicine they check the safety of technologies such as X-rays and ultrasound, provide a national poisons information system for clinicians, and infectious disease surveillance services for NHS Trusts, including monitoring the incidence of TB, MRSA etc. The Agency is also extensively involved in new vaccine development at its Porton lab, seen as vital in fighting potential plagues in an increasingly inter-connected globalised world.

Much of the subsequent debate commenting on public policies was conducted under Chatham House rules and cannot be repeated, but we did think about the need to resurrect robust hygiene practices in a world where many antibiotics are being rendered impotent by resistant bugs, and where climate change could radically change the types of health risks faced by the UK population. The freedom *versus* intervention debate is at the centre of public health policy in the UK.

Liz Bell

The embryo and its future

Recent work within the developmental origins of health and disease (DOHaD) field has shown that changes to the nutritional environment of the early embryo have permanent effects on postnatal phenotype. A whole day was therefore dedicated to this area of research on 14th September 2008 at Seggau Castle, Austria.

The meeting was attended by both early stage and senior researchers from throughout Europe. It brought together both traditional 'DOHaD' scientists and those from research groups not generally associated with the DOHaD hypothesis, for example those involved in developing assisted reproduction techniques (ART).

The first session of the day commenced with a fascinating presentation from Jean-Pierre Ozil (Paris) on calcium oscillations at fertilisation and their importance in long-term developmental competence. Alireza Fazeli (Sheffield) then continued on the theme of pre-implantation development by discussing gamete recognition and communication with the female reproductive tract environment. The workshop then turned to ART, with Nick Macklon (Utrecht) presenting data from his group on how IVF impacts on the developing embryo. Raul Fernández-Gonzalez (Madrid) demonstrated the long-term development and health effects of ART using a mouse model and Mirjam van Weissenbruch (Amsterdam) showed the results of her follow up studies on the health of IVF children.

Following intense discussion of the morning session, early stage researchers presented their work at a poster session with mediated small group discussion. A poster prize was kindly donated by Promega, and this was awarded to Natalia Igosheva from King's College, London for her presentation entitled: *Maternal diet-induced obesity alters mitochondrial function and redox status in mouse oocytes*.

The afternoon then continued with a more traditional DOHaD theme, starting with Adam Watkins (Southampton) discussing how in mice, maternal low protein diet given exclusively during pre-implantation development affects cardiovascular health, behaviour and physiology of the offspring. We then moved from mice to sheep with Kevin Sinclair (Nottingham) demonstrating that reductions in maternal B-vitamins and methionine can epigenetically modify DNA in their progeny and lead to adult offspring with elevated blood pressure and indicators of 'metabolic syndrome'. Ewes exposed to an early gestation global nutrient restriction also produced offspring with altered postnatal cardiovascular function and growth, as presented by Jane Cleal (Southampton).

With all of the discussion focussing on the embryo it was also important to consider the trophoblast component and the developing placenta. Judith Eckert (Southampton) therefore presented her findings on how nutritional status affects trophoblast development in the low protein mouse model. This was followed by Rohan Lewis presenting data from the Southampton Women's Survey. He showed us how the maternal body composition prior to pregnancy affected placental nutrient transport. This concluded the 'Embryo and its future' workshop and everyone headed to the bar at the castle, followed by dinner in Graz. However, we must remember that this workshop would not have been possible without sponsorship from The Physiological Society.

DOHaD

www.dohadsoc.org

Scientific organising committee:

Jane Cleal
Tom Fleming
Mark Hanson
Adam Watkins
Judith Eckert
Rohan Lewis
The University of Southampton, UK.

Quantitative RT-PCR workshop

The 9th Quantitative RT-PCR workshop sponsored by The Physiological Society took place on 7th November 2008 with 18 participants. The workshop is intended as an introduction to quantitative RT-PCR (sometimes referred to as qPCR or real-time PCR). We aim to demystify the technique and demonstrate that it is practicable in any lab with pipettes, a benchtop centrifuge, access to a real-time PCR machine and a modicum of understanding of qPCR principles. Real-time PCR instruments are found in many laboratories these days as their cost falls and the widespread utility of qPCR in a huge range of biological and medical applications becomes appreciated.

These workshops have been run annually since 2001 and have attracted 200 participants in all. The workshop is geared towards those with a basic knowledge of molecular techniques, but little or no practical experience of quantitative real-time PCR. Participants are generally Affiliates of the Society (though a few brave academics have attended)

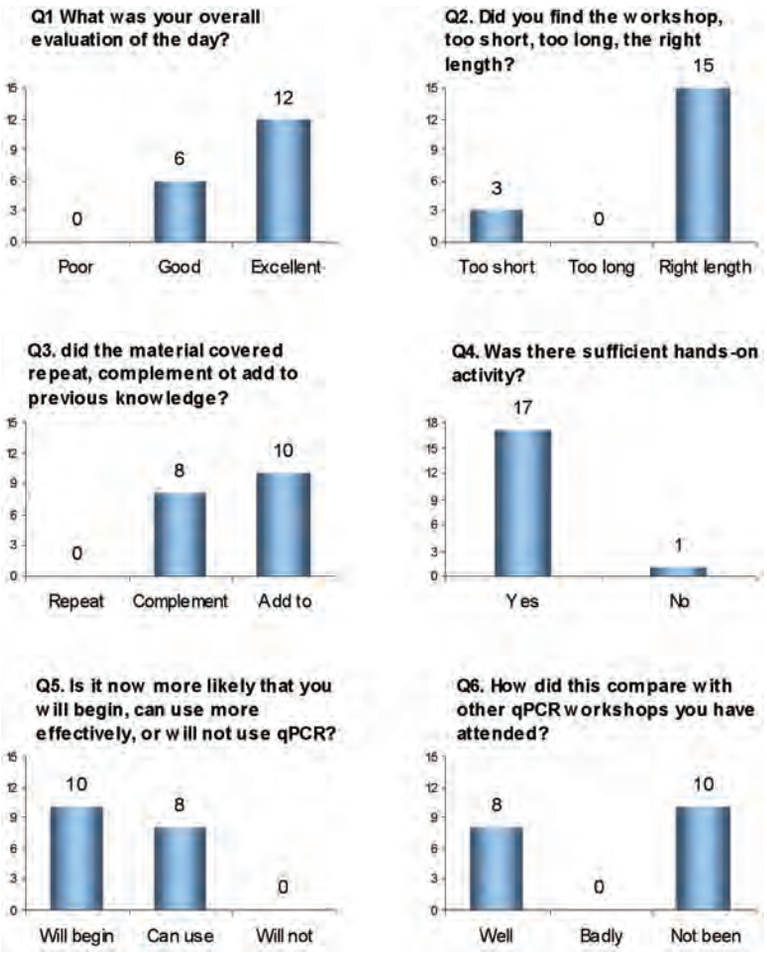


Figure 1. Responses to feedback questionnaire.

and has attracted participants from all corners of the UK and Ireland. The workshop lasts one day and provides hands-on experience of qPCR for each participant interspersed with short talks on various aspects of the technique.

In the practical sessions, participants make a PCR standard for a given gene, amplify these to generate a standard curve using SYBR Green detection of the amplicon, and then use the standard curve to quantify the copy number in unknown samples. Talks include: RNA isolation, assessment of RNA quality and quantity, cDNA synthesis, primer design, amplicon detection strategies, basic trouble-shooting and data normalisation. It's an intensive day but the participants get to generate real data themselves, which most will agree is an important aspect of the workshop.

We have collated the responses to the feedback questionnaire completed by those attending in November 2008 (Fig. 1). To summarise, the vast majority of participants found the workshop to be good or excellent, about the right length, and with sufficient hands-on activity. Of the participants who had attended other qPCR workshops, this one compared well according to all respondents. All participants stated that they would either be able to start using qPCR in their work or would be able to use qPCR more effectively in their research.

If you think you would benefit from attending a future workshop, Dr David Sugden would be delighted to hear from you and will send you details of the next course as soon as they are available.

Email: david.sugden@kcl.ac.uk.

David Sugden
King's College London
Patricia de Winter
University College London

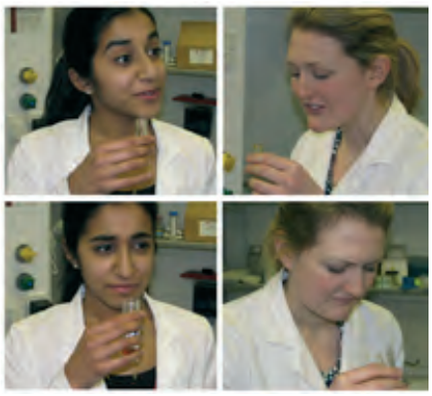
On the menu at the Science Café: 'What the nose knows'

Science Cafés, or Cafés Scientifique to give them their preferred name, are part of a global movement to draw the discussion of science out of the laboratory and into people's lives. According to the Café Scientifique website, these cafés 'are a place where, for the price of a cup of coffee or a glass of wine, anyone can come to explore the latest ideas in science and technology.' (http://www.cafescientifique.org/). The cafés are springing up all over the UK, reflecting a growing popular interest in science and a 'humanising' of scientists. The neurologist and writer Oliver Sacks believes that the Café Scientifique brings science back into culture. Tim Jacob, Professor of Physiology at Cardiff University, is no stranger to discussing his research on the olfactory system through the cultural media of newspapers, radio and television. He was recently invited to take part in a Café Scientifique event in Leeds and I spoke to him about the pleasures and pitfalls of this face-to-face interaction between scientists and the general public.

The overarching theme of Tim's talk was the subject of communication through the sense of smell, which is an ideal topic for the Science Café, as it is of interest to the general public as well as scientists, and has been an area of active research over the last decade. Two to five per cent of the population have concerns or issues regarding their sense of smell and these people have little recourse to standard healthcare. At present, there are very few diagnostic, prognostic or treatment clinics offered through the NHS and treatment strategies are still in the basic research stages. So, even in a small audience there are likely to be one or two anosmic individuals. For these individuals, the lack of a sense of smell presents an untapped reservoir of misery. Anosmia is erroneously perceived not to impact

on everyday life in the same way as other forms of sensory impairment, although Tim would argue against that, and his presentation to the Leeds community outlined the scientific evidence for the physiological and psychological importance of smell.

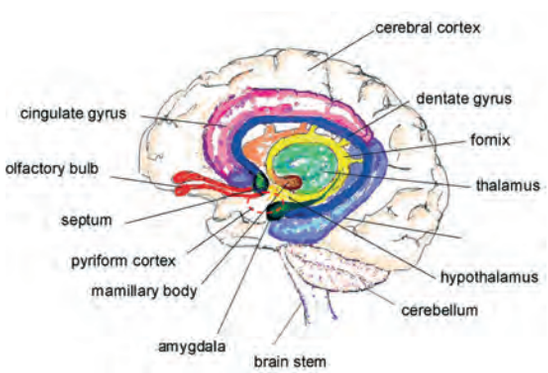
The evening was organised very informally, with the audience seated around tables with their drinks. Despite the quite large size of the audience (around 100), there was an intimate feel to the evening. There was no option for a Powerpoint presentation and, in the absence of any podium or stage, Tim was able wander about between tables as he developed his themes. Without the usual figures and images to lean on, Tim admitted to feeling quite exposed and vulnerable with this 'off the cuff' style of presentation. Luckily he had taken along some 'props' to punctuate his talk: some glass vials containing various odourants – mostly nasty smells that provoke a reaction of disgust in humans that cannot be suppressed! The vials were placed on all the tables and, at appropriate points in the talk, the audience were invited to open them and smell butyric acid (vomit), scatol (faeces), methyl hexenoic acid (sweat) and, as a pleasant experience, santalol (sandalwood). This aspect of the evening certainly broke the ice and prompted people to contribute their own anecdotes. A common theme was the memories evoked by particular odours. One elderly man talked about how a specific combination of smells had opened a locked door in his brain. As a child, he had spent some time in Asia and had learned to speak Chinese. After returning to Britain, as far as he was concerned, he forgot everything he had learned about the Chinese language. Recently, however, he had travelled to Singapore and the street aromas of the city immediately brought his dormant skill to the fore once again.



Physiology students smelling 'nice' (upper panels) and 'nasty' (lower panels) odours in Tim Jacob's lab.

Tim also took along some vials containing the sweat steroid androstenol, a putative human pheromone that is suggested to increase sexual attraction and activity. Tim explains, 'I described the study offering evidence to support this theory, where subjects had worn necklaces containing androstenol around their necks for several days and kept a diary of their 'social interactions' (in the coy terminology of the study's authors (Cowley & Brooksbank, 1991)). After my talk and the extended discussion session that followed, I collected up all my vials of odourant samples, only to find that four of the seven vials of androstenol were missing. Perhaps some members of the audience wanted to conduct their own follow-up studies on sexual attraction! Funnily enough, all the vials of 'nasty' smells were returned and I had to carry them home on the train with me, hoping that the lids had all been put back on securely.'

The extended, interactive discussion session which followed Tim's 40 minute talk ran for over 90 minutes. The audience were friendly and very keen to pick 'their' expert's brains; they wanted to know and to be involved and, unlike most University students, they asked lots of questions!



A section through the brain showing some of the main structures of the olfactory systems. ©Tim Jacob 2007

The Café Scientifique in Leeds is organised by Duncan Dallas, a media science correspondent who also facilitates other science cafés in the UK and, more recently, in Africa. The principles are the same at all the cafés and talks are aimed at a non-specialist, interested audience. At Tim's talk, the audience was limited to 100, and advance tickets were sold as the events are very popular. Although some members of the audience may have come specifically to learn about the science of smell, others attend regularly and get involved in whatever topic is on offer. In 2008, Leeds' Café Scientifique hosted experts to discuss a diversity of topics, including the origin of language, the science of sleep, the impact of the theory of intelligent design, altruism in insects and humans, and the ethics of the relationship between academia and pharmaceutical companies. These events are all run on a shoestring, though. A collection is taken at the end to cover the speaker's expenses – luckily, the Leeds audience had enjoyed Tim's presentation and he was able to pay for his train ticket home!

So, if you are approached to be the expert speaker at your local Science Café, Tim would probably recommend you accept. It was a worthwhile experience for him, albeit very exhausting, because the audience was so interested and responsive. If only all PhysSoc communications could generate this level of feedback...

Sarah Hall
Cardiff University

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Publicising professions: providing career options to post-graduate students

After reading Fiona Randall's article about limited career options in the Autumn (PN72) Physiology News, I felt obliged to write. My perspective is from one who has been involved in offering careers advice on my chosen profession of clinical biochemistry. I felt Fiona's article was a bit negative, since there are a number of options available at the end of any PhD – you just have to look a bit wider. As she mentions, a good place to start are the specially organised days or careers conferences, where a variety of career options are discussed, but no such day can cover every possibility.

For individual professions seeking to recruit graduates, there is always scope for improvement in what we do, but there is certainly plenty happening already. For instance, I have given career lectures on Clinical Sciences careers at the Annual Life Science Careers Conferences organised by the Bioscience Federation (www.bsf.ac.uk). The format of these career conferences has been pretty constant since their inception, except for the inclusion of the now popular CV clinics.

The presence of the Association of Clinical Biochemistry and The Physiological Society at these kinds of events is important for a profession like mine, and has been maintained and encouraged. The duration of a careers fair or lecture is normally limited, and it is therefore important that there is a specific take-home message for interested candidates. One thing that has struck me is that many candidates seem to expect that the job will present itself to them. It doesn't. They have to do their homework and explore a wide variety of possibilities.

These days, the Internet is probably the first port of call for those seeking careers information. A questionnaire submitted to Pre-registration Clinical Scientist Trainees (applicants for clinical biochemistry) during 2002–2004 showed that the Internet was the primary source of careers information for the majority of applicants (Fig. 1). The most popular site visited was NHS Careers (www.nhscareers.nhs.uk) followed by the association's (www.acb.org.uk), which has a thorough subsection on careers.

University departments and career services are also working hard to take the lead and foster partnerships with the professions. Three such partnerships for my own profession are described below. Similar set-ups could be replicated across the country and for different professions – probably they already are. In my experience it is always critically important that local scientists/alumni, especially trainees, are on board and available to offer assistance and advice if required.

Lectures to students are one way for professions to promote their chosen career. For instance, each year the Careers service at Oxford University organises a 'Careers for Chemists and Biochemists' event for 2nd and 3rd year students studying chemistry and biochemistry. Careers adviser Tracey Wells contacts past students and invites them to share their experiences from a variety of professions. In the absence of past students, she has contacted the local John Radcliffe Hospital to ask their junior biochemists to fill in. These events are always well attended, with the venue normally packed to capacity.

Another successful venture is Newcastle University's Graduate Connections database. This is a searchable database of Newcastle graduates working in a variety of careers and organisations. Not only can students read graduates' detailed profiles, they can also get in touch with them directly. This network is a joint initiative between the Careers Service and the Development and Alumni Relations Office at the University of Newcastle upon Tyne.

Finally, I would highlight the recent Pathways event held by Manchester University's Career Service, which stood out as an excellent format for providing finishing PhD students and postdocs with advice and solutions concerning careers options and transferable skills. The Pathways event was different from others that I have been involved in due to the wider variety of subjects covered (not just life sciences). In addition,

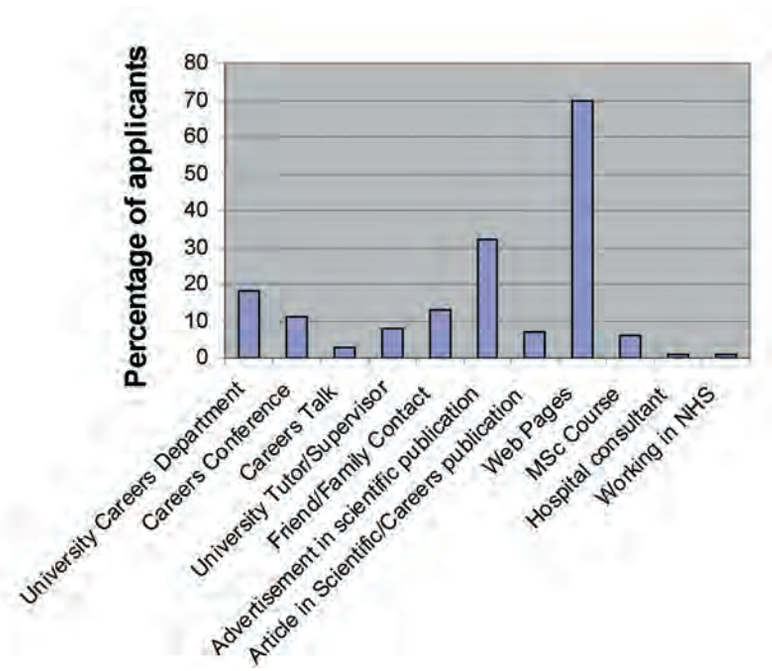


Figure 1. Source of hearing about a career in clinial biochemisty.

it offered skills workshops and Q&A sessions covering selected areas of interest (e.g. health, industry, voluntary, IT, finance etc). I felt that both the speakers and the participants gained a lot from the experience, and it was even opened by a real Dame (Nancy Rothwell)!

If professions want to promote themselves, there obviously needs to be a continued and sustained effort by associated professional and academic societies and their members to raise the awareness of career opportunities. There is usually scope for improvement here – for instance, a recent MORI poll performed for the Royal College of Pathologists showed that only 31% of the public knew pathologists were involved in laboratory testing and diagnoses. The College of Pathologists will soon be the first Royal Medical College to take on the specific task of fostering understanding between society and the medical community. They are addressing this by providing a truly integrated approach to education through the provision of a new Education Centre, which will train professionals, broaden public awareness, and hopefully inspire children.

Schemes and initiatives like these should raise the profile of any profession and discipline. In my own patch, I suspect that the percentage of the public who know of the existence of clinical biochemists is pretty low, and even fewer will know what we actually do! The same is probably true for students considering career option towards the end of their courses.

The career information professions provide to students should be content-rich, whether it be in the form of a careers lecture or website. It should also be targeted to the 'big questions'. For example, at the Life Science Career's Conference, Alan Knott, from University College of St Martins, gives a presentation on teaching as a career. The aim of his presentation is not to make the audience aware of a teaching career, but to dispel the myths and preconceptions of the career being unappealing. As a career option, clinical scientists and other science-based professions are not even starting from the same level of public awareness. Depending on the career, it may be useful exploring the opportunities to raise awareness at an earlier stage in education, especially pre- and post-GSCE where decisions about specialisation are taken which will shape later career options. Readers may already have experiences of such initiatives and should share their experiences and resources – perhaps via Physiology News?

Finally, in her article Fiona discusses job security. Unfortunately, there is no longer the job security that was once available to members of any profession. Even where one can at least be fairly certain overall demand is not going to disappear, such as in healthcare, people are expected to be mobile during the earlier parts of their careers and may have to move several times before securing a long-term post. It is now a fact of life that priorities change in any area of work, and not just in the private sector. For example, in my own bit of healthcare there are limited resources for 'lab-based diagnostics', and with reviews of pathology services at all levels, the provision every post has to be justified.

Tim Lang
Principal Clinical Scientist
Royal Victoria Hospital, Belfast

Fiona Randall responds:

I am grateful for Tim Lang's helpful comments about careers in clinical biochemistry and general careers. My article was aimed at highlighting the difficulties in making it in exploratory research careers in predominantly academia where short-term positions of 1–3 years are common, rather than in specific career posts such as those within the NHS.

There are a lot of careers available to young researchers and I don't know any young researchers who expect jobs to 'find them'. As exploratory scientists we are very lucky to have such an exciting, ever changing field of work and the opportunities to work across the world. I was trying to highlight some of the negative aspects of research careers that could potentially be improved. In the current economic climate everyone is aware that no job is completely secure. Working in an academic lab, morale goes down as the grants come to an end because without money, unemployment looms. For the period of time before the grant ends, there is uncertainty about the future for all people employed on that grant and it seems that every 2 or 3 years your neck is on the line unless another grant comes in. In most jobs, even when times are hard, there is a redundancy package to provide a lifeline if the worst happens. On the other side of the coin, as I have discussed before, a short-term position can be ideal. Being young and single, it is easy for me. I can take the position I want, anywhere in the world. However, it is not so simple for people without flexibility.

Control freak

Patricia de Winter is quite right to complain about faulty scientific design and poor reviewing (Soapbox, *Physiology News* **72**, 9). However, I wonder if it is entirely fair to make these criticisms in a forum where the authors do not have a right of reply. I am not acquainted with any of the authors mentioned and I am not familiar with the journals in question, but if they publish letters that would surely be the normal route. The criticism is then more likely to be read by people who have seen the original article, and editors will normally give the authors the chance to respond in the same issue. I have done this myself many times and I usually find authors very appreciative of constructive comment. At least it shows that someone read the paper!

Stanley Salmons
University of Liverpool, Liverpool, UK

Science funding in the current economic situation

There is no predetermined outcome for science and engineering due to the global financial crisis (*Physiology News* **73**, 3). Decision-makers can either see science and engineering as an investment in the future or a cost to be cut. CaSE will be pushing for policymakers to see an investment in science and engineering as an opportunity to create jobs in the short-term and a way of developing the skills and the ideas needed for the long-term.

So far, the UK's response to the economic crisis has been to fire fight in order to keep the financial sector almost solvent. There has been a small cut in VAT and a fast-tracking of some infrastructure investment. Both will have benefits for research. However, looking across the Atlantic, you see a response to economic crisis that is to be commended. The proposed economic stimulus package in the US has over £10 billion earmarked for science and engineering. President Obama has made science one of his top priorities.

The Prime Minister put the new Science Minister, Lord Drayson, on high-level government committees to make sure that science is considered across government. So far the government has not risen to the opportunity that the crisis provides. Partly this is due to the significant constraints on public expenditure. But a targeted economic stimulus package could have a significant short-term and long-term effect if it focused on skills and infrastructure.

Some of the brightest scientists and engineers went into the financial sector. New bursaries could be created to help them and others re-skill so that they can move into technology sectors, teaching or research. Other opportunities could be created through work placements and training programmes. Rather than losing people to unemployment, funding should be given to up-skill the workforce. This should also be done through increased funding for PhDs and research grants.

Infrastructure projects, like high-speed trains or low-carbon energy generation, could provide both much needed jobs and help tackle some of the pressing issues facing the UK. The Treasury, along with the relevant government department and business would need to work together to make it happen.

The UK has become an international destination for corporate R&D activity. However, once an investment in R&D is stopped, it is often lost forever. It is critical that government support for the financial sector includes pressure for banks to lend money to innovative businesses. If the financial sector becomes risk adverse to scientific and technological developments, the innovative products and companies needed for the economic recovery will not be found in the UK.

How countries respond to the economic crisis will determine how they come out of it. The US looks like it is going to take the initiative and invest in its future once again. It is not enough for the UK to maintain its current commitment to science and engineering. It must redouble its efforts if it wants to be a leader in science and innovation coming out of the crisis.

Nick Dusic
CaSE

Society for Neuroscience

The annual SfN meeting in Washington DC in November 2008 did not disappoint, with the usual plethora of brilliant neuroscience presentations, plenaries and socials. I have focused on a couple of events away from the hard science.

The programme included many aspects of neuroscience away from the lab. SfN is taking every opportunity to encourage members and supporters to communicate about their work. The opening lecture of the conference was an on-stage discussion forum with Mark Morris, a choreographer who works with dance to improve the lives of patients with neurological disorders. Speakers were sitting on stage in armchairs and the lack of scientific figures in the talk made it accessible to any audience and was outside the box of usual conference lectures. Dance classes for Parkinson's disease patients preceded the lecture.

John Morrison's public advocacy forum was particularly topical and interesting with the title Who won the election? Science. The forum was set up to discuss the potential impact of a new President on science and included well-known science policy and political experts. I expected a sum-up of the future directions of American science, including restricted use of embryonic stem cells, but this was never touched on. The main topics of discussion were funding-related and I did not come out feeling optimistic. Like a lot of other important areas, science was flat-line funded under President Bush and, as a result, has been limited. John Morrison highlighted the need for advocation of science in order to get strong research investments. Scientists have a role to educate the law and policy makers, by showing the impact science has on patients' lives. American scientists could do this by creating a network of science advocates; signing up to the SfN advocacy on the society website, meeting with members of Congress to improve relations, holding lab tours or becoming a science advisor to a local representative. Although these are USA-specific ideas, there are ways that UK scientists can educate and improve relations with policy makers. The politicians seemed reluctant to say whether funding for science would increase, but again all members of the forum strongly emphasised the critical need for scientists to influence public opinion on the important implications of their work so that government would be obliged to support them too.

Fiona Randall

Biology in the real world brought the curriculum to life!

Report of the annual conference of the Association for Science Education (ASE), University of Reading, 2009

As part of our schools outreach programme, The Physiological Society (PS) joined forces with the British Pharmacological Society (BPS) and the Biochemical Society (BS) to share an exhibition stand, and to contribute to the 1-day symposium Biology in the Real World: Bringing the Curriculum to Life, at the ASE conference. The annual conference is aimed at all science educators – including teachers, technicians, advisors, consultants and school inspectors – with the aim of improving science education in Britain.

The symposium was organised by members of the Nucleus Group – an informal group of not-for-profit organisations who work together, pooling resources and expertise, to provide curriculum enrichment and enhancement, and careers advice for schools and colleges. Nucleus Group members in addition to BPS, PS and BS who contributed to the symposium this year included: the Wellcome Trust; the Association of the British Pharmaceutical Industry; Microbiology in Schools Advisory Committee; the Society for General Microbiology; the Association for the Study of Animal Behaviour; Royal Botanic Gardens, Kew; Institute of Biology; the Society for Endocrinology and the British Ecological Society.

The Nucleus Group has organised symposia at the annual ASE conference for several years, and uses the conference as an opportunity to help teachers develop and expand on biological concepts and scientific methods they teach in schools, and to inform them of current research in those areas. In view of recent significant changes to key stages 4 and 5 National Curricula, and curriculum emphasis on How Science Works, the 2009 symposium was designed specifically to provide curriculum support and enrichment on new areas of study that may be less familiar to teachers, and to provide ideas of how this knowledge can be used in the classroom, in order to inspire pupils and inform them of the opportunities a career in science can bring. Topics this year were therefore chosen to complement subject areas of the 2009 GCSE and A level specifications.

The symposium was one of the most popular and highly attended events of the conference. The following symposium sessions were expertly chaired by Gail Bromley (Royal Botanic Gardens, Kew): *What is diabetes*? Aileen King (King's College London); *Why do we need a new vaccine for tuberculosis*? Helen Fletcher (University of Oxford); *Drugs of Abuse: psychoactive and performance enhancing drugs*, Emma Robinson (University of Bristol); *What would a monkey do*? Lynda Boothroyd (University of Durham); *Health impacts of climate change*, Hugh Montgomery (University College London) and *Flowers, Forensics and Pharmaceuticals*, Monique Simmonds (Royal Botanic Gardens, Kew). The ideas and information provided in the presentations were skillfully drawn together at the end of the day in an interactive session focusing on How Science Works led by Jeremy Airey (National Science Learning Centres) and Karen Devine (British Ecological Society) in a session entitled *Bringing the Real World into the Classroom*.

To complement the Biology in the Real World session this year, a resource booklet was produced to accompany the symposium. The booklet was produced and designed in-house by BPS, and provides teachers with a professionally prepared hard copy resource which can be used to provide curriculum enrichment in the classroom. The booklet includes a synopsis of each presentation, relevant links to GSCE and A level specification sections, web and other teaching resource links, and web addresses

for careers advice. Feedback from the symposium and conference in general suggests that subject-specific resources of this type are very valuable to teachers, and we received many requests for access to similar specialist literature to complement standard teaching resources in the classroom.

The resource booklet can be downloaded from the BPS and PS websites (www.bps.ac.uk and www.physoc.org/schools).

The Physiological Society appreciates the opportunity that the ASE conference provides to talk to teachers; moreover, sharing a stand with BPS and BS provides an opportunity to pool resources, which together provide an excellent source of information for teachers. The collaborative efforts of our societies, which extend beyond this event, also contribute to developing relationships between the Education Managers; this is important in identifying overlap and in the formation of ideas for future collaborative projects and is useful in terms of promoting the aims of the Biosciences Federation.

We look forward to the 2010 conference, which will be held in Nottingham from 7–10 January.

If you are interested in contributing to The Physiological Society schools outreach programme, please contact education@physoc.org.

Chrissy Stokes
The Physiological Society

Judith Hall
British Pharmacological Society

Hannah Baker
The Biochemical Society

Life Science Careers Conference 2008

On 26 November 2008, King's College London hosted the 2008 Life Science Careers Conference, which was attended by 200 undergraduates and postgraduates from around the UK. The event, organised by member organisations of the Biosciences Federation (BSF), provided information on career opportunities for Life Science graduates – a topic that is considered to be poorly covered by other careers events.

The format for the day included seven talks, one workshop and an exhibition. The talks covered careers from academic research to science communication; the workshop was led by Irrum Magre – The Physiological Society's Education and Membership co-ordinator – who gave an energetic insight into preparing the perfect CV; finally, the exhibition provided delegates with the opportunity to talk to employers, recruitment consultants and representatives of professional bodies.

The event would not have been possible without the generous sponsorship provided by Astra Zeneca with further support from the BSF, The Physiological Society, the Biochemical Society, the Society for Endocrinology and the Society for Experimental Biology.

We have received excellent feedback from delegates, exhibitors and speakers alike, and look forward to running more careers events in the future.

Chrissy Stokes

The BSF Education Colloquium

Organised by the Biosciences Federation (BSF) and hosted by The National Science Learning Centre, this interactive discussion focussed on outreach and enrichment provision by the Biology community. Engaging the next generation of scientists through outreach is high on the agenda at both The Physiological Society and the British Pharmacological Society (BPS), and for this reason both societies were well represented at the colloquium.

With the invitation open to teachers ('customers') and outreach providers ('practitioners') alike, the programme held high promise for us to learn what constitutes effective outreach in biology 'from the horse's mouth'. However, enthusiasm was dampened when it became apparent that the number of teachers attending the event was very low; no doubt this reflects the obstacles faced by teachers to secure teaching cover for continuing professional development (CPD) and similar activities.

As Director at the National Science Learning Centre, John Holman opened proceedings. Professor Holman highlighted factors that he considers to be the key influences to the number of individuals studying STEM and the numbers gaining strong STEM qualifications. It was clear that there are specific areas where our societies could have an impact: professional development for teachers, careers advice, and enhancing and enriching the curriculum and particularly targeting the first 3 years of secondary school (key stage 3). Indeed, both societies are already very active in the latter two of these areas.

The two talks that followed Professor Holman's came from individuals actively involved in science outreach. Karen Bultitude (University of the West of England) talked in detail about the STEM directories, which provide a coherent resource signposting the 'customers' to UK-wide outreach activities in all STEM subjects. Jeremy Pritchard's (University of Birmingham) talk addressed science outreach from the perspective of an academic; sharing anecdotes from his own experience and highlighting the benefits of science outreach, he was perhaps preaching to an already converted audience. However, it was interesting to share his experiences of how best to approach outreach aimed at different levels of education.

The remainder of the day had been designed to encourage active communication between the delegates, each having the opportunity to sign up to 2 of 5 possible workshops: Teacher–Scientist Networks (TSNs), Junior Café Scientifique, Working with STEMNET, Science Learning Centres or Good practice in university outreach. Each session focussed on a different aspect of science outreach with a discussion facilitated to enhance interaction on the topic in question. Without many teachers in each of the groups, feedback from the customers was limited.

Dr Phil Smith and Claire Willis led an interactive, role-play workshop on 'Teacher–Scientist Networks'. Founded in 1994, there are now over 240 teachers and 80 scientists on the scheme, which links single teachers with individual scientists with the aim of establishing long-term partnerships in order to encourage students to engage with contemporary science. The TSN scheme was set up and runs in Norwich and is funded by the Gatsby Charitable Foundation and other organisations. Claire Willis described her work as a TSN coordinator responsible for a scientists at work scheme in the North East of England.

Phil Waywell stood in at short notice to describe his work with Junior Café Scientifique. The junior version, founded by Pablo Jensen, builds on the success of the popular and established Cafe Sci to promote a mechanism by which young people can discuss scientific issues in an informal environment. The discussions are student-led and individual Cafes are arranged, publicised and run by the young people themselves, giving them ownership of what they learn. In an informal situation, the focus is on discussion, not debate or learning,

consistent with the underlying feeling that classrooms are for lessons; cafes are for conversation. Students choose their own topics and then invite an expert (who could be a scientist or, for example, a science journalist) to the discussion. Examples of topics discussed so far include: eating disorders, designer babies, aliens, Dr Who, time travel, heroes, drugs, stem cells, could men have babies?, and perhaps the most intriguing, how do you get holes in crumpets?

Delegates attending the Working with STEMNET workshop had the opportunity to learn more about how STEMNET has evolved and is now outsourcing much of the work to outreach partners. The workshop was facilitated by Harriet Dow and Steve Hutcheon, both working with the North Yorkshire Business and Education Partnership Ltd (NYBEP), which holds the STEMNET contract for North Yorkshire. NYBEP, like other contract holders, has excellent links with local businesses and schools. Through this network, NYBEP coordinates outreach to all secondary schools in the local area; it provides strategic advice and individually tailored services to help schools and colleges enrich the curriculum, businesses engage actively in the development of their future workforce, and learners better understand their personal skills and future choices. As a contract holder, NYBEP coordinates over 100 Science and Engineering Ambassadors (SEAs) working in the North Yorkshire area. Steve Hutcheon works as a SEA for NYBEP, and shared with the group some of his experiences; he also facilitated the group discussion on what makes outreach effective, the challenges we face and the importance of evaluating success and how best to gather this information. One of the strongest messages delivered in this workshop was for outreach to be considered effective the impact within the classroom must be long lasting.

Jeremy Airey, a Senior Professional Development Leader at the National Science Learning Centre, facilitated a discussion on how Science Learning Centres operate to provide teachers with CPD. Whilst it is undeniable that the courses offered by the SLCs offer invaluable training and 'thinking' space away from the classroom, getting the time away is both difficult and expensive. The message from this workshop was that CPD must help develop the teachers, not simply train them; it is important to ensure that the training is taken back to both students and colleagues for capacity building and long-term effect. Again, evaluation was considered to be central to ensuring future CPD success. Jeremy was keen to stress that CPD courses run at the nine regional learning centres and in the national learning centre, and the over-arching aim is to share teaching methods and skills and knowledge.

The importance of Good Practice in University outreach was covered in a final workshop, and the day's proceedings were expertly wrapped up by Sue Assinder (Chair, BSF Education Committee) who brought together the various topics covered during the day in an audience-led survey from the perspective of the various stakeholders represented in the audience.

Learned societies are, of course, only a small part of the network working to support science education and, whilst it is important we continue to develop our own strategies and activities to support enrichment and enhancement, we must be careful not to re-invent the wheel but to contribute to and complement external programmes where appropriate.

National Science Learning Centres: www.sciencelearningcentres.org.uk

Bioscience Federation: www.bsf.ac.uk

Teacher scientist network: www.tsn.org.uk

STEMNET: www.stemnet.org.uk

Researchers in residence: www.researchersinresidence.ac.uk

Scientists at work: www.slcne.org.uk

Chrissy Stokes
The Physiological Society

Judith Hall
British Pharmacological Society

Prize Lectures 2009

The Physiological Society is delighted to announce that the following Prize Lectures will be delivered in 2009:

Annual Review	Stephen G Waxman	Physiology 2009, Dublin, July
Bayliss–Starling	Gero Miesenboeck	Physiology 2009, Dublin, July
Biller	Gavin Stewart (*held over from 2008*)	Newcastle Themed Meeting, September
GL Brown	Mark Boyett	Various (see the website for schedule)
Hodgkin–Huxley–Katz	Eric Kandel (*held over from 2008*)	Physiology 2009, Dublin, July
Michael de Burgh Daly	Colin Nurse	Physiology 2009, Dublin, July
Paton	Diethelm W Richter	Physiology 2009, Dublin, July

The Annual Public Lecture will be delivered on 8 July at Physiology 2009 in Dublin by Stephen O'Rahilly, and will be entitled '*My genes made me eat that*!'

The Wellcome Lecture, which was instituted in 1985 and supported by funds from the Wellcome Trust, has been discontinued. Special thanks go to the Wellcome Trust for their support over the years.

The Journal of Physiology

Earlier in the issue, David Nicholson, Journals Publishing Director at Wiley-Blackwell, writes about the Publishing Workshop in Beijing, jointly organised by The Physiological Society and the American Physiological Society. David Sheppard, *The Journal of Physiology* Editor who took part in the Workshop, gave subsequent presentations at other universities at the request of Chinese colleagues and reported that his presentations 'were to packed lecture theatres of staff and students hungry to learn about publishing their work in international biomedical journals'. The capacity attendances at these events and the manifest enthusiasm of the attendees underlines how important it is to make journal requirements clear to potential authors, especially those from parts of the world unfamiliar with how publishing in the western world works.

The 15 February issue of *The Journal of Physiology* contains an editorial by Gordon Drummond (Drummond, 2009) entitled 'Reporting ethical matters in *The Journal of Physiology*: standards and advice' which has been written specifically with this aim in mind. In his article, Gordon begins by explaining why *The Journal* sets its particular requirements – as an international broad-scope journal reporting basic physiological research, with no article size restrictions, *Journal* policies are designed to ensure that all details concerning animal experimentation are clearly stated and confirm to UK legal requirements.

The article then goes on to elaborate on how animal experimentation is regulated in the UK. This information is already available on government web sites, and links are provided to these, but a mass of information is summarised clearly and succinctly, which will be particularly helpful for researchers from other countries who aspire to publish in *J Physiol*. Useful information on US regulations and the differences between US and UK regulations is also provided. Common problems in submitted papers are identified, highlighting how carefully *Journal* Editors scrutinise submitted manuscripts to ensure that policies are adhered to and all necessary details are reported.

A section on human studies provides background information and how this relates to *The Journal*'s reporting requirements. Regulations and standards concerning reporting, coercion, and use of human tissue and embryos are all covered and the significance of the *Declaration of Helsinki* is explained.

Finally the article sets out *The Journal*'s publication ethics policies. These largely reflect the guidelines laid down by the Committee on Publication Ethics (COPE). *Journal* policy on entitlement to authorship and author contributions, conflict of interest, plagiarism and redundant publication and image manipulation are summarised to give authors clear, concise information on what *The Journal* considers to be unacceptable practice.

Carol Huxley

Reference

Drummond GB (2009). Reporting ethical matters in *The Journal of Physiology*: standards and advice. *J Physiol* **587**, 713–719.

Going down the YouTube?

Since the last issue of *Physiology News* went to press the ongoing decline of the newspaper and magazine industry in the USA has intensified as economic conditions have worsened. To get a flavour of the magnitude of the problem, watch the 'Morbid Major Magazine Song' on YouTube which lists all the magazines that have folded in recent years. Are there any messages for journals from this sorry story? Phil Davis, a former librarian at Cornell University, thinks so. In his blog for the Society for Scholarly Publishing Phil reflects that the fate of the newspaper industry is largely the result of unrealistic consumer expectations: they want everything online, now, free. This leaves newspapers with a problem: how to fund the validation process that they traditionally offered their readers through expert reporting and comment. The result is likely to be a pared-down industry that provides 'news' though online links to citizens' 'journalism' sites such as Twitter and YouTube.

Readers of academic journals have similar perceptions – financial deals between research institution librarians and journals publishers behind the scenes leave journal readers with the impression that access to journals is unfettered and free. However, an increase in genuinely free-to-reader content as a result of author-pays publishing options and the growth of institutional repositories hosting author manuscripts could persuade librarians that they don't need to pay for journals any more. Could journal publishing suffer the same fate as the US newspaper industry? Or, conversely, what is different about journal publishing that is still worth paying for? Phil dissects the function of journal publishers and suggests that registration, certification, distribution and archiving are the essential functions. His list can be debated (perhaps 'quality control' would be a better term than 'certification') but it is harder to dispute his assertion that all functions bar certification are now being offered, free, by repositories. He concludes by urging journal publishers to cherish the function that – at present – only they can offer readers: certification through peer review.

Only days later Phil posted an article on a scandal among French geologists who have been bringing peer review into disrepute by reviewing the work of colleagues in the same institution. It seems that some journals are not being careful enough about standards of peer review. The Editorial in the autumn issue of PN explores varying standards and concludes 'this is no time to get sloppy'.

The previous article on the facing page draws readers' attention to a recent editorial in *The Journal of Physiology* by Gordon Drummond outlining the ethical standards set by *The Journal*'s Editorial Board for both animal experimentation and

publication. The Board expects similar high ethical standards in its review process. These standards are well known to Editors of both Society journals and are published in the *Instructions to Authors*. Nevertheless, with increasing accessibility to and hence awareness and scrutiny of the processes of academic publishing via the internet, it is probably time to make them clearer for authors, readers and reviewers. We are working with our publisher Wiley-Blackwell to create web pages concisely and unambiguously stating our review and publishing standards that can be accessed easily by anyone interested in how journals are published.

Carol Huxley

Experimental Physiology
Translation and Integration

New Editors for 2009

Mark Chapleau

Mark received his PhD in Physiology from Louisiana State University in 1985. Following postdoctoral research training at the University of Iowa Cardiovascular Center under the mentorship of Dr Francois M. Abboud, he joined the faculty at the University of Iowa. He currently holds the rank of Professor in the Departments of Internal Medicine and Molecular Physiology & Biophysics, and has a joint appointment at the Veterans Affairs Medical Center in Iowa City. Mark's research focuses on neural mechanisms that regulate blood pressure and cardiovascular function in physiological and pathological states. Current studies are addressing the molecular basis of baroreceptor mechano-electrical transduction; the role of reactive oxygen species and other signalling molecules in sensory transduction and sympathetic neurotransmission; and mechanisms responsible for impaired autonomic nervous system function in hypertension, heart failure and ageing.

Daniel Green

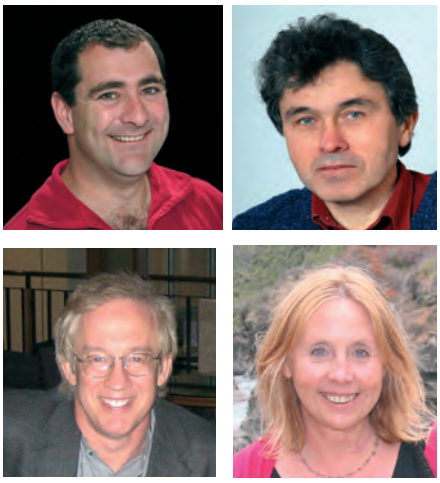
Danny currently holds dual appointments as Professor of Cardiovascular Physiology in the Research Institute for Sports and Exercise Science at Liverpool John Moores University and in the School of Sport Science, Exercise and Health at the University of Western Australia. His research revolves around the impacts of exercise and other preventative measures on macro- and microvascular function across the lifespan in humans. He completed his PhD work in Cardiology at Royal Perth Hospital under Roger Taylor and then spent some valuable time working with Mike Joyner at the Mayo Clinic. In recent years he has collaborated closely with Professors Gerry O'Driscoll (Cardiac Transplant Unit RPH) and Tim Cable (LJMU).

Sergey Kasparov

Sergey received his MD at Moscow Sechenov Medical Academy where he then stayed to do a PhD in Pharmacology and later progressed to Docent (Reader). In 1994 he obtained a Doctor of Sciences degree from the Russian Academy of Sciences. He was a recipient of the Alexander von Humboldt Fellowship and worked at Max-Planck Institute of Psychiatry in Munich. Sergey moved to the UK in 1996 and currently is a Reader in Molecular Physiology at the Department of Physiology and Pharmacology of Bristol University. His recent work focused on the role of non-synaptic communication in central autonomic control, including the role of nitric oxide and monoamines. He has pioneered research based on the use of cell-specific viral gene expression and dedicates considerable efforts to the development of new molecular and imaging techniques. Much of his work is based on international collaborations with colleagues in USA, France, Australia and Russia.

Susan Wray

Susan Wray studied Physiology at University College London (UCL) for her BSc. She remained there and studied the changes in the expression of genes in the connective tissue of the uterus for her PhD. She continued working on the uterus but switched to study the myometrium where she investigated the link between metabolism and contractility. She moved to a lectureship in Liverpool in 1990 where she began to work on the control of intracellular pH and calcium concentration in both uterine and vascular smooth muscle. Working with Ted Burdyga, she is applying confocal microscopy to the study of cell signalling in smooth muscle. She has recently stepped down from being Head of the Department of Physiology and is currently engaged in setting up the Centre for Better Births, a grouping of scientists and clinicians studying the mechanisms behind problems of childbirth resulting from abnormal uterine contractility. A former Editor of *The Journal of Physiology,* she is looking forward to joining the Board of EP.



New *Experimental Physiology* Editors, clockwise from top left: Daniel Green, Sergey Kasparov, Susan Wray and Mark Chapleau

In the new issue

In addition to original Research Articles, the first two issues of Experimental Physiology 2009 contain: the 2008 Paton Lecture by Michael Spyer – *To breathe or not to breathe? That is the question*;
A Hot Topic article by Julian Paton, John Dickinson and Graham Mitchell – *Harvey Cushing and the regulation of blood pressure in giraffe, rat and man: introducing 'Cushing's mechanism'*;
and Reports from the Symposia
– *Cotransmission in the autonomic nervous system* and
–*Mouse models for human epithelial disease: novel insights and new horizons*

BIOSCIENCES FEDERATION

Goodbye to the Biosciences Federation – hello to the Royal Society of Biology ?

I recently attended an Extraordinary General Meeting of the Biosciences Federation (BSF), at which an enabling motion to dissolve the BSF and to merge with the Institute of Biology (IOB) to form a new biological society was debated and unanimously agreed. This was followed later in the same week by endorsement of this motion at an EGM of the IOB. Subsequently, an Interim Council has been established to put in place the detail that will allow the new organisation to be launched successfully in the second half of next year. The final decision on forming the new organisation will be made at the BSF AGM in April. So what will this new organisation look like ? What will be its aims and how should The Physiological Society interact with it ?

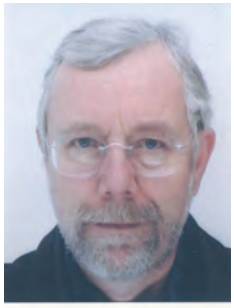
The plan proposed at the EGM is for the new society to obtain a Royal charter and call itself The Royal Society of Biology (RSB). Whether the 'Royal' status is a good or a bad thing probably depends on your politics and on whether you think the 'Royal' attitude to new developments in biology is helpful; however, it will impress many and would place biology on a comparable footing with, for example, chemistry (Royal Society of Chemistry).

The new society will be a hybrid with about 12 000 individual members (who are currently with the IOB) and about 50 member societies of the BSF, such as The Physiological Society. It's an interesting membership mix and one wonders how the new organisation will address the needs of its two, rather different, constituencies. The council of the new society will be comprised of members elected by member societies, those elected by IOB members and others selected by the council to add additional skill sets. The council members elected by member societies will need to be people with a wide understanding and appreciation of the issues that affect a range of biological sciences. They will need to cover areas from molecular biology to intact organisms and from microbes through fungi and plants to animal and human biology, not forgetting interfaces with medicine and with a number of important bioscience industries. Nancy Rothwell will be the chair of an Interim Council that will guide the formation of the new organisation. I am sure that Nancy is well aware of the issues facing Physiology and Physiologists (she is an honorary member of The Society); however, I am also sure that she will act in the best interests of all the organisations and members, without favouring one sub-group.

A draft business plan of the 'RSB' was provided prior to the EGM and gave a valuable insight into the aspirations of the new organisation. To quote:

'The vision for the RSB is a unified organisation capable of nurturing the biological sciences, serving the interests of biology and speaking with an authoritative voice on biological aspects of the scientific, educational, economic and social issues of the day. It will increasingly co-ordinate and integrate its activities with those of its autonomous member organisations.

Richard Dyer.



Mike Collis.

An early review of strategic priorities will enable it and its member organisations together to achieve critical mass and a more visible profile in key areas of representation, outreach and education. In these ways it will benefit biosciences in the UK and internationally, work in the public interest and provide value to its membership'.

The most important objective for the RSB will be to achieve financial viability. Neither the IOB nor the BSF are in a strong financial position. The BSF is dependent on contributions from its member organisations, and The Physiological Society has been very generous in this respect giving £20k a year for the last 3 years and providing office accommodation and IT support. The IOB has assets, such as its offices in London, and some cash reserves from membership subscriptions, but it also has a significant liability to its pension fund. The precise amount of this liability is hard to define; at worst case it could swallow most of the current assets of the IOB or at best case leave more than £1 million to support the RSB. A key priority for the RSB will be to increase individual and organisational membership numbers in order to achieve financial viability. It has set itself some challenging targets, with an increase in individual membership from 12 000 to 13 500 and in organisational membership from 75 to 100 in its first year. It will also aim to achieve an income of £100k in the first year from specific funded projects and thereafter achieve a 50% per annum increase in this type of funding.

In addition to representing the biological sciences, the RSB will aim to provide educational and outreach

activities, particularly utilizing the extensive branch network of the IOB to promote biology in schools and by engaging with local development agencies. It plans to establish a representative in every secondary school and relevant university department and to be represented at all major science fairs and festivals in the UK. The Physiological Society also aims to have a representative in every relevant university and already has an established network of university representatives. We must ensure that unhealthy competition does not develop between ourselves and the 'RSB' but rather that our strategies and activities are complementary.

A very understandable aim of the RSB is to develop effective communications by developing its current publications and building a useful website. The business plan includes an aim to harmonise the content and publication dates of member organisations' house journals. I will be interested to hear the views of the Editorial Board of Physiology News on this proposal. The RSB also hopes to be recognized as a leading authority on key scientific publishing issues, and this will be achieved through the influence and expertise of member organizations such as The Physiological Society that have a significant presence in scientific publishing. I do not think that the RBS has ambitions to launch a new scientific journal.

The IOB currently has a significant CPD programme and awards a number of membership categories such as Membership and Fellowship of the Institute of Biology and Chartered Biologist status. These titles are obviously important to the IOB membership and the RSB plans to maintain and develop these and to continue to enhance the status of the Chartered Biologist. Only 30 of our ~2800 members are MIBiol, FIBiol or CBiol, which indicates that these titles are not particularly prized by physiologists. A further goal is to generate a membership database including all RSB individual members and those of collaborating learned societies and other member organizations. There are issues to be dealt with here in terms of privacy, data protection laws and security and these would have to be resolved satisfactorily before The Physiological Society would agree to this.

One person who will not be an officer of the new RSB organisation is Richard Dyer. He will step down as CEO of the BSF at the end of July and has stated that he will not seek to be appointed as CEO of the new organisation, because he thinks a younger individual is needed. I like and respect Richard, and although I sometimes find that we disagree, I think that he has done a great job in making the BSF a much more effective 'spokesperson' for member societies. I can see his high level vision for a single society representing and supporting UK biology (much in the mould of the Royal Society of Chemistry) underpinning the aspirations of the RSB. I shall miss his presence in our offices and his provocative and thought provoking statements and newsletters.

The council of The Physiological Society has discussed the RSB business plan and supports the formation of this new society as an organisation that acts as an authoritative voice for biology with Government and the public and that supports biology education in schools. Will the day come when The Physiological Society and other major learned societies will want to merge more of their activities into the RSB and move to a single society like the RSC ? I do not currently see any enthusiasm from our council or from our Members to do this, as it could risk us losing our separate identity, our influence and would be a drain on our resources. If the RSB becomes very successful and influential, however, we may want to reconsider our position.

Mike Collis

Memorable technicians

In 1971 I passed the 2nd MB examination and was offered a place in Professor Vernon Pickles's Physiology Department's Honours School in Cardiff. The Final Year Honours Class was taught solely by Dr SL Stone: his course included twice weekly practical classes in mammalian physiology; the decerebrate cat was the standard preparation. Stone's personal technician was Mr TJ Surman (known to all as Nam: Surman, Namrus, Nam) who was completing his last year's work in Stone's laboratory and in the Hons class: he was 68 years of age. Surman's career began in 1918 in Oxford in Sir Charles Sherrington's department and he learnt his techniques from Mr George Cox, Sherrington's personal technician. Surman moved with Professor Graham Brown to Cardiff in 1924 and 47 years later was still there. He had arrived as Senior Technician, was rapidly promoted to Chief Technician, and held that post for nearly 45 years. An interview with Surman was published by Tilli Tansey in an early issue of The Physiological Society Magazine (1997, **26**, 27). Surman was then approaching 90. The Hons class used Sherrington's *Mammalian Physiology* (Surman preferred the first edition!) and we repeated a great many of the classic exercises set out in that splendid book. It may be that few since 1973 (Stone died in 1973) have undertaken such a course of instruction. The combination of Stone's extraordinary knowledge of physiology and exceptionally critical mind, and Surman's technical virtuosity was remarkable, and testing!

Before joining the Honours School it was suggested that I should work as a junior technician to improve my practical skills: I did so from June until October 1971. This introduced me to Surman, a very formidable figure, and to Mr Ben Jenkins (who had taken over from Surman as Chief Technician), Mr Dennis Brown and Mr Bill Barry. All three had been appointed by Surman before the Second World War and each had given more than 40 years service to the department. Through them I met Les Jones, Chief

Technician, Department of Anatomy, one of the finest histology technicians of his time. Under Ben Jenkins's tutelage I learnt to grease burette taps (properly!) using the chopped up red rubber tubing dissolved in hot Vaseline that Surman favoured over commercial products, to wash mercury (with soap and water: how else?), to varnish benches (properly!) and to make up Ringer solution in large quantities. Smoking kymograph papers, especially the extended version favoured by Stone, was a 'Surman Special': it was said that only a man with arms as long as his could place the smoked paper on the apparatus single handed. Surman was an artist with the Haldane apparatus (he much preferred the original to the later models) and was a demanding teacher.

Surman's skill in decerebration may have been becoming rare by the 1970s: I do not remember a poor preparation. In the Hons practical examination each candidate was allowed the assistance of a technician: Surman 'assisted' me and I suspect that any success I achieved in the examination was in large part due to him. I recall working out some results with a slide rule (easier, I thought, than the log tables provided) and the sniff of distain as Stone looked over my shoulder. Physiologists who trained in mammalian physiology were lucky indeed if they trained with people like Stone and Surman.

Robert L Maynard
Health Protection Agency

Get involved and write an article for *Physiology News*

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

Standing up for Science

There is a massive public appetite for science and particularly in how the body works, what we should be eating or what we can do to prevent disease. Newspapers are full of headlines such as 'New fears over leukaemia link to coffee' or 'Blood 'test which can predict disease' is unveiled'. Some of this information can be misleading, and even dangerous and as a community we have become increasingly aware of how important it is that scientists counteract misinformation and take on the responsibility of being involved in public debates about science. But it can sometimes be hard to see how to do this, or whether your background is relevant, particularly if you are at the beginning of your career.

Over 5 years ago, *Sense About Science* noticed that the voice of early career scientists was missing from public debates. When we asked them why they were not involved, we found that whilst most were very passionate they didn't know how to get started, what opportunities were available or if their voice would count. To address this we set up workshops to allow early career scientists to find out directly from journalists how the media works and to interrogate them on why headlines do not match stories, why is science sexed up and how they can work together. The workshop participants also hear from scientists who have been at the frontline of media interviews about their experiences and what to expect if your research hits the headlines.

Past workshop participants have formed the Voice of Young Science (VoYS) network, which has grown to over 400 early career scientists from a range of backgrounds but all with the common goal to tackle pseudoscience in the public. Last year, fed-up with the increasing misuse of science to sell products, VoYS decided to look into these claims – from Pret's claims its food contained 'no obscure chemicals' to a Ski yoghurt that 'optimises the release of energy from food'. They contacted the manufacturers to try and track down any evidence to support these claims, but in all cases they found there was none. Even more shockingly, it seemed that none of the companies had anticipated anyone would ever question these claims.

The results of the VoYS investigation was released in a dossier, *There Goes the Science Bit*... which was reported by both national and international media. The intention was not only to make companies aware that someone would hold their claims to account, but also to encourage others to ask these questions. Over the last year, the support for this work has grown with more people joining them and the VoYS forum buzzing with endless examples of other pseudoscientific product claims.

Looking at these examples, VoYS noticed an increase in the use of scientific terminology that had little or no scientific meaning to sell products. The word 'detox' stood out in particular, as it was being used to advertise everything from teas to hair straighteners. The network decided to find out what the companies meant by 'detox' and what evidence they had for their claims. They found that detox was meaningless and many of the claims the companies made about how the body works, such as 'toxins have built up in the body', were wrong and even dangerous. They decided to address these claims head-on in a leaflet, *Debunking Detox*, which made the anti-detox promise: 'Your body is capable of removing most potentially harmful chemicals you will encounter in your daily life'. On the 5 January, braving the snow, they stood outside chemists explaining to passers-by that the best thing you can do after Christmas is have a glass of water, a good night's sleep and trust your body to do the rest.

This campaign has only just begun as VoYS want to make the 'detox' claim a marketing embarrassment, not a marketing advantage

VoYS members have also been pursuing different activities to stand up for science in public, from online podcasts to writing letters to newspapers. To help forge recognition of how much impact both little and big steps can have on public debates about science, they have shared their experiences in a new publication, *Standing up for Science 2* – the nuts and bolts in which they recount what works and what does not.

Ultimately they want to send the message that it really matters that scientists stand up for science in public and no matter what your background is, there are always things you can do to raise the standard of science in debates.

To get involved or find out more about VoYS workshops and projects, please contact Alice, VoYS Co-ordinator, at voys@senseaboutscience.org . In 2009 the Standing up for Science media workshops, sponsored by The Physiological Society, will be held on the following dates: 27 March (Manchester), 8 May (London), 19 June (London), TBC October (Edinburgh).

Why not allow a mouse the freedom of the countryside?

'I reckon no mouse be thoroughly miserable unless he be condemned to live in a transgenic mouse house'

A mouse owned by Jonathan Swift

We often hear biotechnology criticised – transgenic mice in particular are thought to be sinister and dangerous. Animal rights fanatics tell us they are a cruel and pointless intellectual diversion and a technological prelude to human eugenics. Environmentalists have differing concerns; they believe that the mice will escape from the confines of their cages, pollute the British countryside with aggressive transgenes and mutate a range of British wildlife. I once spoke to an artist who expressed far more sensible concerns – he explained that transgenic mice caused unnecessary conflict in the art world as surrealists loved, but aestheticists hated, the famous photograph of a human ear growing on a mouse's back.

This transgenic hysteria has unforeseen consequences. In order to give a poor transgenic mouse a job, a home or even an existence, I have to work in the Guantanamo Bay of the mouse world. It's a place where mice disappear. They go in and don't come out. Other mice don't know that they are there. Even their bodies are quietly burned. It has carded entry, alarms and nice little aluminium security barriers that evil scientists can break their legs by falling over, but mice can't climb without a ladder.

This is because a few unsavoury elements in British society (actually our government) needlessly worry that the odd mouse might escape and cause transgenic armageddon. All it does in reality is create more excuses for bureaucracy and cost a fortune.

And as for the potential ecological armageddon generated by a tidal wave of transgenes swarming their way across the British countryside and entering the genomes of weasels, stoats and owls, the actual results would be erm...absolutely great.

Consider the ecological milieu forming the backdrop to a classic English countryside novel, a Thomas Hardyish tale, gentle but dark earthy peasant romance with a tragic ending. The vegetation usually provides a stunning backdrop with myriad shades of green, luxuriant foliage and yellow cornfields with swathes of lovely looking red poppies. There is just one real problem. The wildlife it pallid, boring, not nearly sinister enough and totally fails to add any real air of exotic literary menace.

A few stray transgenes could enliven English wildlife and the classic countryside novel no end – imagine *Tess of the d'Urbevilles* real nemesis being a transgenic weasel called Alec. The whole thing could spread to other classic countryside novels. Imagine Ratty in a post genomic *Wind in the Willows* – he could have a great time explaining to toad that his behavioural problems, including a fondness for drink, were caused by insertion of a testosterone receptor motif box into his serotonin receptor gene, one he acquired from cannibalising an escaped mouse.

I would like to experiment with the enlivening of the English countryside by initially releasing two strains of transgenic mice, two potential transgenes of the apocalypse. The initial genes would be a jellyfish luminescence followed by the narcolepsy gene.

Luminescence

Luminescent genes from jellyfish literally have the potential to brighten up the countryside. In my ideal world, luminous mice would be encouraged to escape from the mouse house and then be fed to barn owls. This could produce one entirely fortunate side effect – a nocturnal, luminous, low-flying

predator. This could be a fantastic fillip for the tourist trade: around the summer solstice swarms of new age 'psychically over-sensitive types' might pay good money to see a luminous owl (sacred to the Druids, of course) fly silently over Stonehenge.

Narcolepsy

Someone has deleted the orexin gene from a very fortunate mouse: any stress, threats or even a heavy lunch and the mouse has an attack of narcolepsy and simply nods off. Lucky little bugger; I wrote to the authors of the paper volunteering myself as their first human subject. An excellent transgene that needs the freedom to wander around the English countryside! What that gene could do to a range of wildlife. Somnambulist buzzards, even foxes with sleep disorders. And the ultimate in vertical gene transfer, squirrels that suddenly nod off to sleep, fall out of a tree and land unconscious on the heads of passing tourists.

If this initial experiment is successful, there is a further range of transgenes that I would love to see released. Japanese scientists have deleted one gene that renders mice unafraid of cats, there is a PEPCK-C^{mus} mouse that can run for 6 hours without a break, and there is a mouse with dopamine receptor alterations that cannot respond to cocaine (an advantageous evolutionary trait in inner city areas), any of these could change the intra-species dynamic of the entire countryside.

Do you think I might need a permit?

Dr Keith Cormorant is about to lose his Home Office licence

Keith Lucas (1909)

The "all or none" contraction of the amphibian skeletal muscle fibre.
J Physiol **38**, 113–133

Keith Lucas FRS (1879–1916) may be justly regarded as the founding father of British biophysics. Working at the Cambridge Physiological Laboratory, he produced an astounding body of work in little more than a decade from 1904 to 1914. Though he died tragically young, Lucas' influence in physiology and biophysics survived him, notably in the work of his pupils AV Hill and EH Adrian, both later to win the Nobel Prize. In addition, Lucas' mastery in constructing novel and highly sensitive experimental apparatus can be seen as launching a tradition in UK (and perhaps specifically Cambridge!) physiology which reached triumphant fulfillment through the achievements of later workers like Hodgkin and Huxley.

The 1909 paper is an example of the use of the frog nerve–muscle preparation, still widely in use – in larger variants like the sciatic nerve–gastrocnemius muscle – in undergraduate physiology teaching. The paper follows up a famous earlier work which employed direct electrical stimulation of the same small cutaneus dorsi muscle (Lucas, 1905). The 1909 paper extends this approach, familiar to modern investigators, of using a very small, and carefully chosen, experimental preparation in order to reduce the number of biological 'components'.

Lucas describes how he picked the frog cutaneus dorsi muscle because a colleague (a Dr Anderson), had pointed out that the muscles were innervated by only a very few nerve fibres: 'On examining the nerve which supplies the *cutaneus dorsi* I found that the number of large medullated [motor] fibres constituting the minute nerve trunk is not more than nine or ten…'

He goes on to give a description clearly recognizable as the muscle 'motor unit' concept: '…if each nerve-fibre, when excited at all, caused the contraction of all its twenty or so [innervated] muscle-fibres, then the preparation might be regarded as consisting of eight or nine units, *each unit being a nerve-fibre with its attached muscle-fibres*.' (italics added)

Of course, recording the contraction of such a small muscle, while stimulating the nerve with precisely determined adjustable amounts of current, was not a trivial task in 1909. Here Lucas was aided by his other stand-out talent as an instrument designer and maker. To quote Lucas's Royal Society obituary: 'His mastery of the design of new instruments, coupled with his capacity of making what he wanted, gave him great power in the art of experiment…'

Lucas concludes as follows:
'The small number of motor nerve-fibres… affords an opportunity of enquiring whether it is possible by grading the stimulus applied to a nerve-fibre to obtain graded contractions of the striated muscle-fibres which each nerve-fibre supplies.

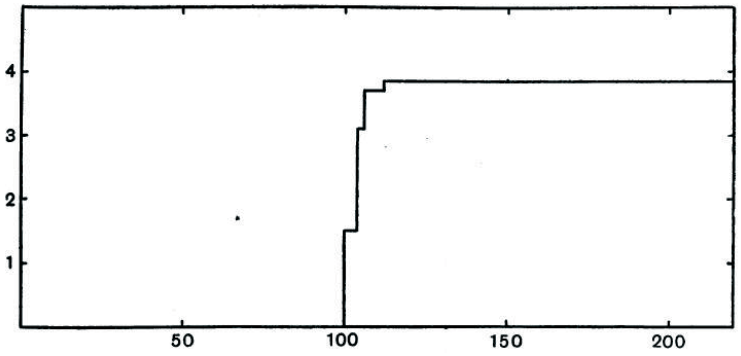


Figure 1. Lucas' plot of stimulus strength (*x*-axis) *vs* muscle contraction (*y*-axis).

It is found that when a series of stimuli of increasing strength is sent into the nerve… the contraction of the muscle increases in a few definite steps. When once a step has been established further increase of the stimulus causes no further increase of the contraction until a new step is reached… [see Fig. 1]

Presumably each step in the increase of contraction means that another nerve-fibre… has been excited, and that the muscle-fibres to which that nerve-fibre runs have consequently contracted. It follows that in each muscle-fibre the contraction is always maximal regardless of the strength of stimulus which excites the nerve-fibre…

The 'submaximal' contraction of a skeletal muscle is the maximal contraction of less than all its fibres.'

Lucas' last paper, published posthumously, was found in manuscript among his papers with the annotation 'finished Aug 3rd 1914'. The next day the German Army invaded Belgium, and Britain declared war on Germany. Lucas volunteered for military service, and was about to enlist as an infantry private when his technical virtuosity got him 'diverted' to the Royal Aircraft Establishment. Here he rapidly improved the design of aircraft compasses, among other technical achievements, and also proved such a successful leader that he was commissioned in the Royal Flying Corps as a Captain in charge of a section of 400 men. Wishing to learn to fly in order to further his work on aircraft technology, he undertook pilot training. Tragically, he was killed in a mid-air collision over Salisbury Plain on 5 October 1916, aged only 37.

After Lucas' death his widow Alys changed the family name to Keith-Lucas. Their three sons, born in 1910–12, all grew up to become Professors, in social work, aeronautical engineering and local government. Still more Professors can be found among Keith Lucas' grandchildren, including botanist Michael Keith-Lucas of Reading University, with yet more scientists in the generation after that. Keith Lucas himself was the son of a notable engineer, and grandson and great-grandson on his mother's side of mathematicians and naval navigators. His scientific great-grandchildren thus represent the sixth or seventh generation of scientists in a remarkable family line.

Austin Elliott

Reference

Lucas K (1905). *J Physiol* **33**, 125–137.

Wilfred F Widdas

1916–2008

Wilfred Widdas was a stalwart of The Physiological Society; a Member for over 50 years he was on the Editorial Board of *The Journal of Physiology*, and was its chairman (1970–72). He was assiduous in attending Society meetings even into old age, sitting near the front and always keen to contribute to discussion – sometimes in a blunt style that somewhat baffled those speakers who assumed the supremacy of textbook orthodoxy. Wilfred lived to see the atomic structures of molecules that underpinned processes that he had obtained theoretical insights into more than 50 years ago – this is discussed by Richard Naftalin. His willingness to think against the current grain, to embrace mathematical reasoning and to exploit quantitative prediction in cell physiology were characteristic of his personal, idiosyncratic style. Indeed his attempts to explain biological phenomena with physical mechanical analogues may have their Victorian roots via his own link to Faraday.

His more recent writings on muscle contraction (the most recent 'A reconsideration of the link between the energetics of water and of ATP hydrolysis energy in the power strokes of molecular motors in protein structures ' published only this autumn), and on the role of surface tension and water evaporation in protein conformation changes remain speculative, but are full of ideas that may yet challenge future experimentalists.

Much less abstruse but characteristically profound were his contributions to placental and fetal research. He started in this field in the late 1940s when as a young (medically trained) demonstrator at St Mary's Hospital Medical School in London he assisted his then Professor, A.S. Huggett, in work on a variety of experiments all related to fetal growth and its control. Following his move to his own department at Bedford College, University of London, he wrote in 1960 his last contribution to this area, a masterful yet brief review on 'Transport mechanisms in the foetus' for the British Medical Bulletin. His insights pithily summarized in this article remain incisive and relevant: thus, conceptually placental transport was seen to be distinct from transcapillary exchange with respect to mechanism; for the placenta, colloid osmotic forces were less important than those set by non-colloids, and it was the transport processes for these solutes, specifically for amino acids and for sugars that needed understanding. Widdas predicted that these processes would involve facilitated diffusion mechanisms – mechanisms of the type originally proposed by Widdas himself in his classic 1952 paper in *The Journal of Physiology*. That paper had appeared in the September issue of *The Journal*; the August issue had contained 'A quantitative description of membrane current' (all 44 pages) by two young physiologists working in Cambridge, individuals who set the scene for the heroic era of post-war UK physiology. It has to be relevant to the physiological community of today – scattered as it now is in the UK within many different academic communities – that both of these papers, that of Widdas as well as that of Hodgkin & Huxley, remain widely cited two generations later. Will the insights of articles in today's 'high impact factor' journals wear as well?

Wilfred Widdas (who died on 23 October) with Graham Baker (photo by Martin Rosenberg,1999).

Richard Boyd
Brasenose College, Oxford

Richard Naftalin writes:

To members of The Physiological Society Wilfred Widdas is synonymous with erythrocyte glucose carriers, GLUTs as they are now called. He was at the forefront of the twentieth century drive to bring the rigour of physical sciences to the description of biological processes. This reductionist approach to Biology has had its fair share of success over the past 60 years and Wilfred's work certainly has been very influential in shaping our current views on biological transport processes.

Despite a late start, delayed by World War II, during which he served as a doctor in the Royal Army Medical Corps retiring at the rank of Major in 1946, having qualified in Medicine at Newcastle in 1937, Wilfred had a long career in Physiology.

It started 2 years after being demobilized when he was awarded a studentship, for ex-service doctors to undertake PhD training in the Physiology department of St Mary's Hospital under the supervision of Prof A. Huggett FRS. His primary field of study was glucose transport across the sheep placenta. It was then thought that glucose crossed like oxygen from mother to fetus by passive diffusion down its concentration gradient i.e. glucose $\text{flux}_{mf} = k(S_m - S_f)$ where S_m and S_f refer to either glucose concentration in maternal or fetal blood. It became evident that although at low concentrations glucose could cross the placental barrier as a linear function of the glucose concentration gradient in either direction, at higher concentrations, the transport rates were consistent with a hyperbolic relationship between flux and glucose concentration. At high concentrations the glucose $\text{flux}_{mf} = k(1/S_f - 1/S_m)$.

Today, saturation kinetics is an everyday concept routinely taught as part of every first year biology course. But back in 1950 it was new departure. At the start the analysis of experimental data involved quite a lot of serious maths –well beyond the grasp of most physiologists at that time – or this. However, in addition to his medical degree, Wilfred

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Image courtesy of Darragh Shane Bracken

Native Bolivian children at the Sun Island on Lake Titicaca, La Paz (3827 metres above sea level) (Giussani, p. 24)

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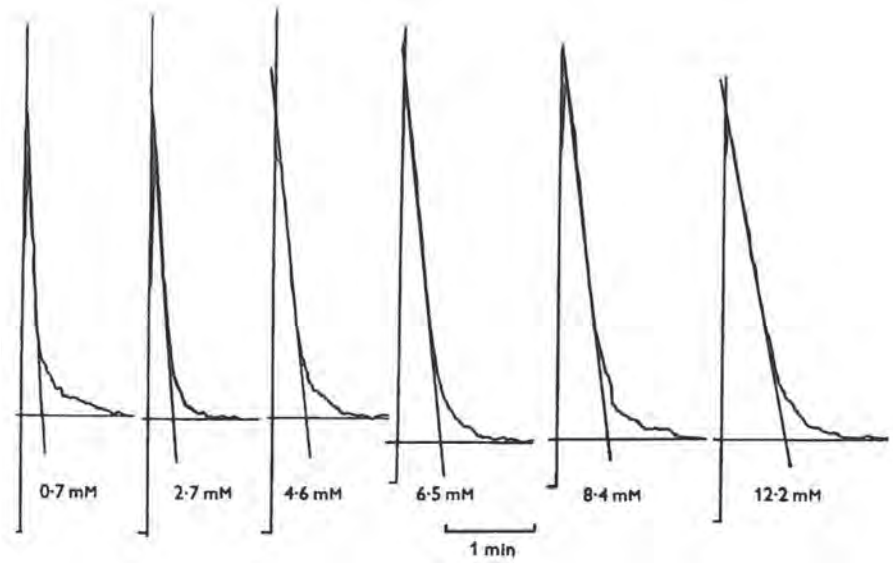

Figure 1. Tracings of a series of records from the photo-electric apparatus during 'exit' experiments at 37°C and pH 7.4. Cells equilibrated in 76 mM glucose were losing glucose into media containing glucose at the concentrations shown. The linear part of each record has been produced to cut the base line, and the time from injection of the cells to this intersection was measured for analysis of the results (from Sen & Widdas, 1962*a*).

had obtained an external London University degree in mathematics, so was well able to formulate the integral equations required to describe the time courses of net glucose movements across the placenta. In that far off age, when the slide rule was at the cutting edge of technology, even with his degree in maths, this was a considerable feat, which was under-appreciated by the majority of his contemporaries, who perhaps were more excited by descriptions of electrical transients in nerves and muscles coming from Cambridge and UCL than by the more sedate changes in blood sugar in fetal sheep reported from St Mary's Medical School.

We tend to think of Wilfred Widdas as an aloof establishment figure and he certainly became that: Foundation and only Professor of Physiology at Bedford College, London; Editor of *The Journal of Physiology*; member of the Senate of London University and Chairman of the Board of Studies in Physiology, London University.

However, it was not always so. In a rather bitter note to Physiology News (**65**, 10) Widdas describes how his theory of mediated diffusion of glucose was initially rejected by

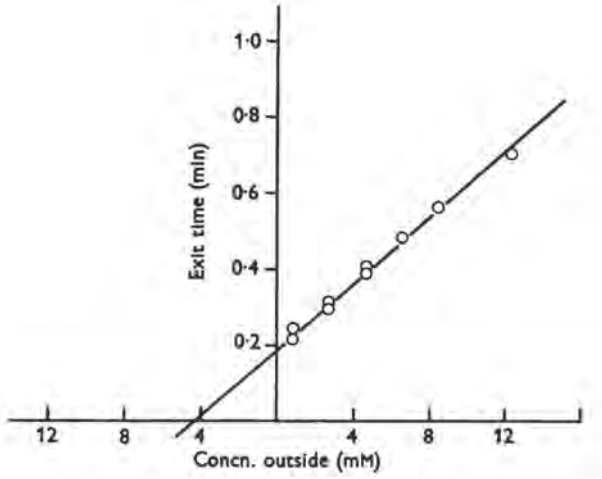

Figure 2. 'Exit' times obtained from the records described in Fig. 1 plotted against the concentration of glucose in the outside media. The line (drawn by eye) gives two intercepts; that on the ordinate represents the time (to) which would have been taken for exit into a glucose-free medium and that on the abscissa gives the concentration of glucose into which the exit time would be twice to (from Sen & Widdas, 1962*a*).

establishment figures at University College London (amongst whom was E. J. Harris, discoverer of ATP consumption during muscle contraction – and as a later claim to fame, supervisor to such worthies as Roger Thomas, my colleague Robert Hider and yours truly).

It was only after Fisher and Parsons working in Oxford had applied saturation kinetics to description of sugar flow across the intestine (Fisher & Parsons, 1953) that Widdas was permitted to publish what were to become his classical papers on analysis of glucose transport in placenta (Widdas, 1952, 1954).

These early studies are exemplary in their clarity, attention to detail and depth and breadth of understanding and prescience. These qualities apply to all Wilfred's work published in *The Journal of Physiology*. His papers that reached a wide following were those initiated in King's College London with A.K. Sen, but completed at Bedford College (Sen & Widdas, 1962*a*,*b*).

This work adopted the methodology of Orskov (1935) to monitor the volume changes of human erythrocytes suspended in isotonic solutions by change in light scattering. The method had also been used by Wilbrandt (1938) and LeFevre & LeFevre (1952) to monitor rates of hexose sugar inflow and exit from erythrocytes. They were one of the first direct means of recording an electrically silent phenomenon, which had been clouded both by laborious calculations using difficult maths needed to work out the rates and by tedious and imprecise chemical analysis of cytosolic sugar content.

Widdas's elegant and simple studies brought much needed precision to the ideas of how sugars move across the cell membrane.

The diagrams in Figs 1 and 2 show how Widdas used the Orskov method to obtain the infinite – cis K_m at 37ºC, later termed, the 'Sen–Widdas K_m' by W. D. Stein (Stein, 1989). Figures 1 and 2, taken from Sen & Widdas (1962*a*), show that increasing the glucose concentration in the external

bathing solution to 4 mM reduces the initial rate of glucose exit from cells containing 76 mM by half. If glucose were transported by diffusion then the concentration needed to reduce the initial rate by half would be 38 mM.

The hyperbolic relationship between the glucose concentration in the external bathing solution and the inhibition of glucose as illustrated in Fig. 2 suggests that glucose reversibly binds to an import site on the external surface of the cell membrane for glucose entry with a K_m of ≈ 4 mM. This glucose entry slows the rate of net glucose exit, which is the difference between exit and entry fluxes.

A conceptually simple way to explain saturation kinetics was in terms of a carrier which had the properties of ligand recognition and translocation from side to side. According to Widdas 'Lundegardh (1940) appears to have been the first to suggest that molecular components of the membrane may be involved in such transfers' (Widdas, 1952). This concept, first called the ferry boat model by Ussing (1952), was generally adopted in the 1950's to explain, first, the saturation kinetics and then selectivity of the transporter. The reason for preference for a mobile carrier over a fixed site transporter was the phenomenon predicted by Widdas in his 1952 paper on glucose transport by the placenta of uphill countertransport. This was first demonstrated elegantly by Rosenberg & Wilbrandt (1957). They argued that a fixed site model does not permit the possibility of uphill counterflow of a labelled by the downhill counterflow movement of an unlabelled ligand whereas a mobile carrier does. This argument together with the similar phenomenon now termed 'accelerated exchange' (LeFevre & McGinniss, 1960), where the rates of sugar exchange measured by isotope fluxes are observed to be much faster than the maximal rates of net flux, has been considered as crucial evidence in favour of mobile sites in the long running debate as to whether glucose transport is via a number of fixed sites occluding

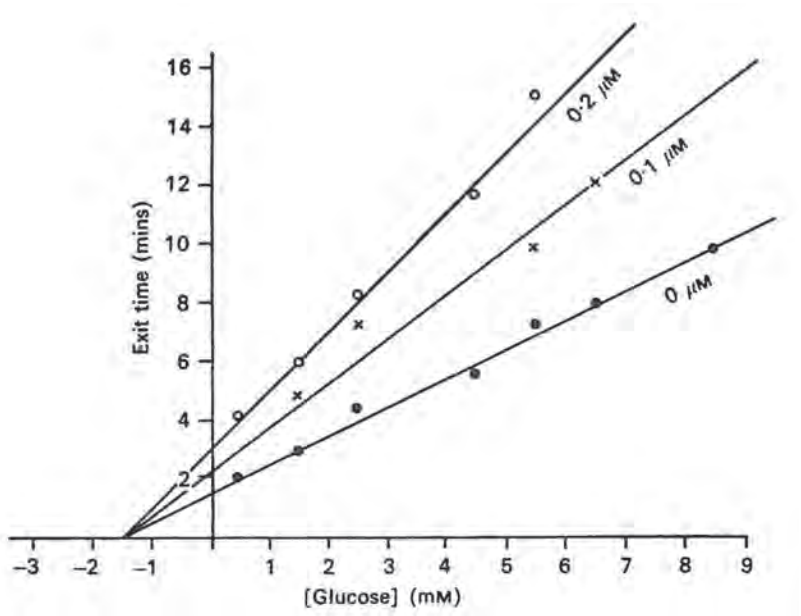

Figure 3. Effect of outside glucose concentration on glucose exit times in the absence and presence of Cytochalasin B at 16°C. Points • exits in control experiment, points x exits in the presence of 0-1 μM Cytochalasin B, points o exits in the presence of 0.2 μM Cytochalasin B (from Basketter & Widdas, 1978).

a channel or via a single site with alternating exposure to either side of the membrane.

The next important study Widdas undertook which combined the Orskov method with monitoring of isotopically labelled sugars was a demonstration by kinetics with David Basketter that cytochalasin B and phloretin, both known to be powerful inhibitors of glucose transport, act at different sides of the transporter. Cytochalasin B acts as a non-competitive inhibitor of external glucose exit (it does not affect the

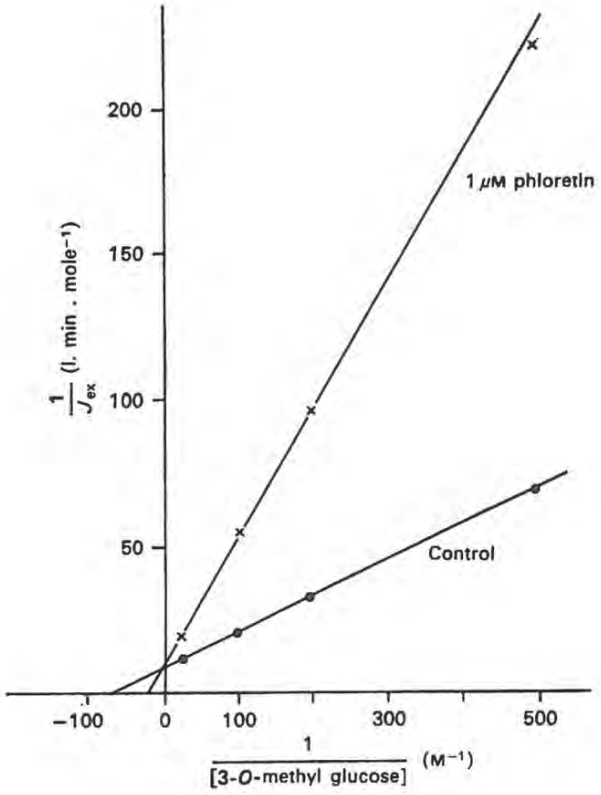

Figure 4. Lineweaver-Burk type plot of 3-*0*-methyl glucose exchange in the range 2-40 mM in the absence and presence of 1 μM phloretin. Points • control exchanges, points x exchanges in the presence of 1 μM phloretin. Points represent mean of two experiments (from Basketter & Widdas, 1978).

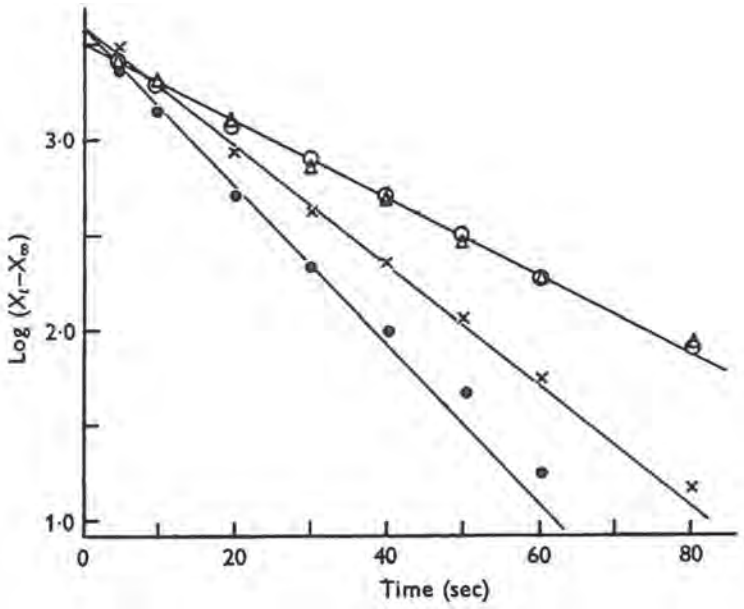

Figure 5. Effects of ethylidene glucose on the loss of intracellular radioactivity during glucose exchange at 20 mM (16ºC) plotted logarithmically. Points • control experiment: points x 50 mM inside: points o 200 mM inside: points Δ 25 mM outside. The slopes of such lines were used to derive the exchange flux as described in the text (from Baker & Widdas, 1973).

K_m at the external site (Fig. 3), but as a competitive inhibitor to glucose exchange flux, mainly controlled by glucose binding to the internal site. In contrast, phloretin and maltose, a non-penetrating dissacharide, act as competitive inhibitors at the external site, but as non-competitive inhibitors of exchange (Fig. 4) (Basketter & Widdas, 1978).

A key long-term collaboration Widdas had was with Graham F. Baker, who studied as an undergraduate, PhD student and then as post doctoral colleague. This collaboration with Graham continued after Graham moved to a lecturing post at Royal Holloway, Egham which amalgamated with Bedford College until Graham's untimely death in 2006.

The most important work of Baker and Widdas together, in my view, was their demonstration of the asymmetric affinities of the glucose transporter. This was first shown unequivocally using the non-transported, but permeant inhibitor 4-6-*O* ethylidene-D-glucose. The half-saturation concentration for ethylidene glucose inside the cell was estimated at *ca* 110 mM, whereas on the outside the value for exchange inhibition was ca 11 mM (Figs 5 & 6).

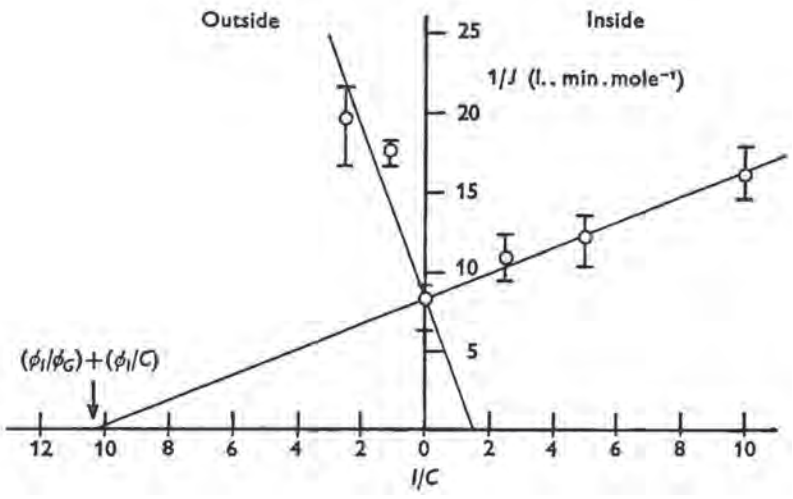

Figure 6. Reciprocals of glucose exchange fluxes (at 20 mM and 16ºC) at different concentrations of ethylidene glucose (relative to that for glucose). Points on the right were means (and range of 3 to 5 results) with the inhibitor inside the cells. Points on the left were means (and range of 3 results) with the inhibitor in the outside medium. Control point mean and range of ten results. Intercepts on the abscissa depend on the ratio of the half-saturation constants but also contain the term Φ_I/C (from Baker & Widdas, 1973).

The possibility of asymmetric transporters was first mooted by Widdas in his earliest papers (1952, 1954) The transport theories for carrier-mediated glucose transport formulated dialectically by Widdas and a few contemporaries quickly became the mainstays of the thin scaffold of evidence supporting the alternating site carrier theories of passive solute transport. It was also incorporated into symporter and antiporter theory. With very few dissenters, these models have become the dominant paradigm for biological transport mechanisms.

Although he dedicated most of his long and very distinguished academic career towards defining and refining how glucose crosses cell membranes, Widdas was very aware that kinetics is a remarkably ambiguous science which requires linkage to a firm structure to acquire credibility. Latterly, in his post-retirement years at Royal Holloway, Widdas attempted to rationalize the kinetic studies on glucose transport by projecting them onto the emergent 2- and 3-dimensional structures of transport proteins. Some of this later work has proved remarkably prescient, like his early kinetic studies.

Despite his widespread influence on transport theory Wilfred never had a large scientific budget or became part of the scientific nomenclatura, which now, more than ever before, decides on what and who will prosper. During most of his working life the bulk of his equipment was home-made or consisted of ex-military cast-off pen recorders, of which he was very proud. One wonders if he could have survived today.

As a man and physiologist Wilfred Widdas was indefatigable, continuing his work literally until the very last. He will be remembered, admired and respected by those who knew him for being both irrepressible and irreplaceable.

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Anthony Carruthers writes:

Wilfred Widdas and I met several times during my graduate study at King's College London. These meetings were occasioned by gatherings of the London membrane group and often found Wilfred, Graham Baker and Richard Naftalin engaged in discussions about their

Wilfred (at the back) with colleagues at Helmsley Hall, 1940–41.

recent findings or, if fortune smiled, discussing some of my data on sugar transport in squid giant axons. Listening to these three engaged in data interpretation opened new horizons for me by illustrating the cut and thrust of scientific discourse and by redirecting me to an evolving literature on the theory of protein-mediated solute transport across cell membranes.

Wilfred Widdas was a shy, modest man but possessed of deep insights into glucose transport. It was not surprising, therefore, to learn that Wilfred's contributions to the field of glucose transport were numerous and transformative. His work, along with that of Paul LeFevre and David Miller, forever changed the study of glucose transport from phenomenology to a quantitative science. He used the tools emerging from the simple but profound recognition that transporters are enzymes that translocate substrates between cellular compartments to develop and critically evaluate new hypotheses for sugar transport. More importantly, his contributions provided the foundation for others to build upon as the field grew and theories for transport multiplied. Wilfred's most important papers remain absolutely relevant to and revealing of the complexities of sugar transport. These include: (1) the defining 1952 opus describing saturable sugar transport and an alternating carrier transfer mechanism (Widdas, 1952); (2) the first consideration of a transport mechanism that simultaneously presents extra- and intracellular sugar binding sites (Baker & Widas, 1973); (3) demonstrations of asymmetric affinities for sugar transport inhibitors and techniques for determining inhibitor sidedness (Basketter & Widdas, 1978). These ideas coalesced into a 1980 review of sugar transport (Widdas, 1980) that remains both germane and a delightful read. Wilfred Widdas was a catalyst who legitimized the study of non-electrolyte transport, who offered the first description of the alternating carrier model for sugar transport that is so influential among today's biochemists and who remained true to the idea that theory must explain behaviour even at the cost of rejecting theory. Those of us who work in the field of non-electrolyte transport have lost a revered colleague who pioneered the foundations of our field.

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Gerald Elliott also writes:

Wilfred Widdas was the most charming and helpful of the people that I met after I arrived at King's College London as a very 'green' young Demonstrator in Physics in 1954. He was Reader in Physiology and a stalwart of the Mixed Common Room. Incidentally, contrary to some accounts of the Rosalind Franklin story, this facility existed happily alongside the male-only room and was very pleasant; the male one seemed rather less welcoming, being then dominated by a group of what we would nowadays call rather 'fogey-ish' young lawyers and historians

Wilfred taught me to order Dover sole on Fridays when available, and showed me how to dissect it. He told me he had been a Royal Army Medical Corps doctor during the war, perhaps because I had mentioned that I was completing my National Service in the Territorial Army. It was not until after his death that I learned that he had been plucked from the beaches of Dunkirk and returned to England by a minesweeper that had been sunk on a subsequent trip.

Wilfred described himself then as basically a simple medical man, a

Wilfred Widdas (1974) at the Delhi Congress, with AK Sen.

description he always reiterated whenever it was appropriate. Our meeting came just after the publication of his seminal *Journal of Physiology* paper mentioned elsewhere in these accounts. As a young physicist just starting in biology I am sure that I did not recognize his distinction at the time. However, I was very aware of his friendship, which meant a great deal to me, and of his encouragement and interest in all aspects of the science that went on at King's.

Though I was delighted for him, I was personally a little sad when Wilfred was appointed Foundation Professor of Physiology at Bedford College, since it meant we no longer saw him so often at King's. I greatly missed his company at lunch, though I continued to see him at Physiological Society meetings and enjoyed talking to him whenever we met. I recall that after Bedford merged with Royal Holloway we would sometime talk about the buildings of the merged College at Englefield Green, which I had visited in my childhood, and which were famously (and incongruously) modelled on a Loire Chateau.

The second phase of my interaction with Wilfred began 40 years on, when I wrote to congratulate him on being elected an Honorary Member of The Physiological Society in 1994. By this time I was well aware of his many distinctions. In particular, having come across his paper *Developments in sub-microscopic physiology* (*Biomedical Letters*, 1993, **48**, 15–27) I also knew that he was interested in biological machines. I sent him copies of some publications of my own on muscle contraction, and this initiated a 14-year correspondence between us about biological motors that was terminated only by his death on 23 October last year.

This correspondence had us agreeing on some things, but arguing about others. In retrospect, I am slightly sad that we tended to focus more on our disagreements – there was much that we did agree on, and it is a pity that we did not pursue these aspects further. As for the disagreements, as I understood it Wilfred was convinced that muscle contraction, and other biological phenomena, involved the interplay of two energy sources, these being the surface energy of water and the usual energy derived from ATP. I did not find his arguments on this point totally convincing – for me at present it is 'not proven' – although it is quite possible Wilfred may eventually turn out to have been correct. I am reluctant to try to summarize his ideas any further because in one of the last emails he sent me, about 2 weeks before his death, he wrote 'Here you go again, misquoting what I wrote and then arguing that the concept is unclear to you'. I was abashed because he went on to say that this was a technique that he had encountered from diverse referees, and that generally led to his papers being rejected – I too have often been on the wrong end of this phenomenon! Interested readers can find Wilfred's own account in the open access journal *Int J Mol Sci* (2008, **9**, 1730–1752), which is the paper we were currently discussing. Subsequently he developed what he called his 'wheelbarrow view of physiology' for me. This was related to a point that he made in his last letter to *Physiology News* (Winter 2008, **73**, 36) where he took issue with a rather sloppy shorthand statement on thermodynamics made by some crystallographers. As will be seen from that letter, Wilfred felt that earlier correct science (he cited Wallace Fenn's 1920s work on muscle) was too often subverted and misunderstood by subsequent workers.

Captain WF Widdas.

I spent the last part of October at my French holiday home for the cider-making season, and on the all-day ferry ride back to England I had a long think about a 'gedanken experiment' that I would put to Wilfred to take our discussion forward on the topic of the interaction and inter-conversion of biochemical energy sources. I intended to base this on the first electric motor invented by Michael Faraday, because I knew Wilfred was proud of his illustrious family forebear. Coming to my computer the next morning to write to him I was shocked and saddened to learn of his death. My last attempt to take Wilfred out to dinner a few years ago, in tribute to those long-ago King's College Dover soles, had been thwarted by his physical frailty and dietary regime. However, this frailty emphatically did not extend to his mental processes, as our email exchanges testified. In understanding, in intellectual capacity and in sheer energetic involvement Wilfred Widdas was at his best until the very end. For the second time in my life I shall miss him dearly.

The Society also notes with regret the deaths of:

Pavel Hnika, a Society Member since 1966.

Margarethe (Gretel) Holzbauer-Sharman, a Society Member from 1962.

Hans Friedrich Meves, a Society Member since 1965. He was a Member of *The Journal of Physiology* Editorial Board from 1977 to 1984.