PHYSIOLOGY NEWS

summer 2010 I number 79

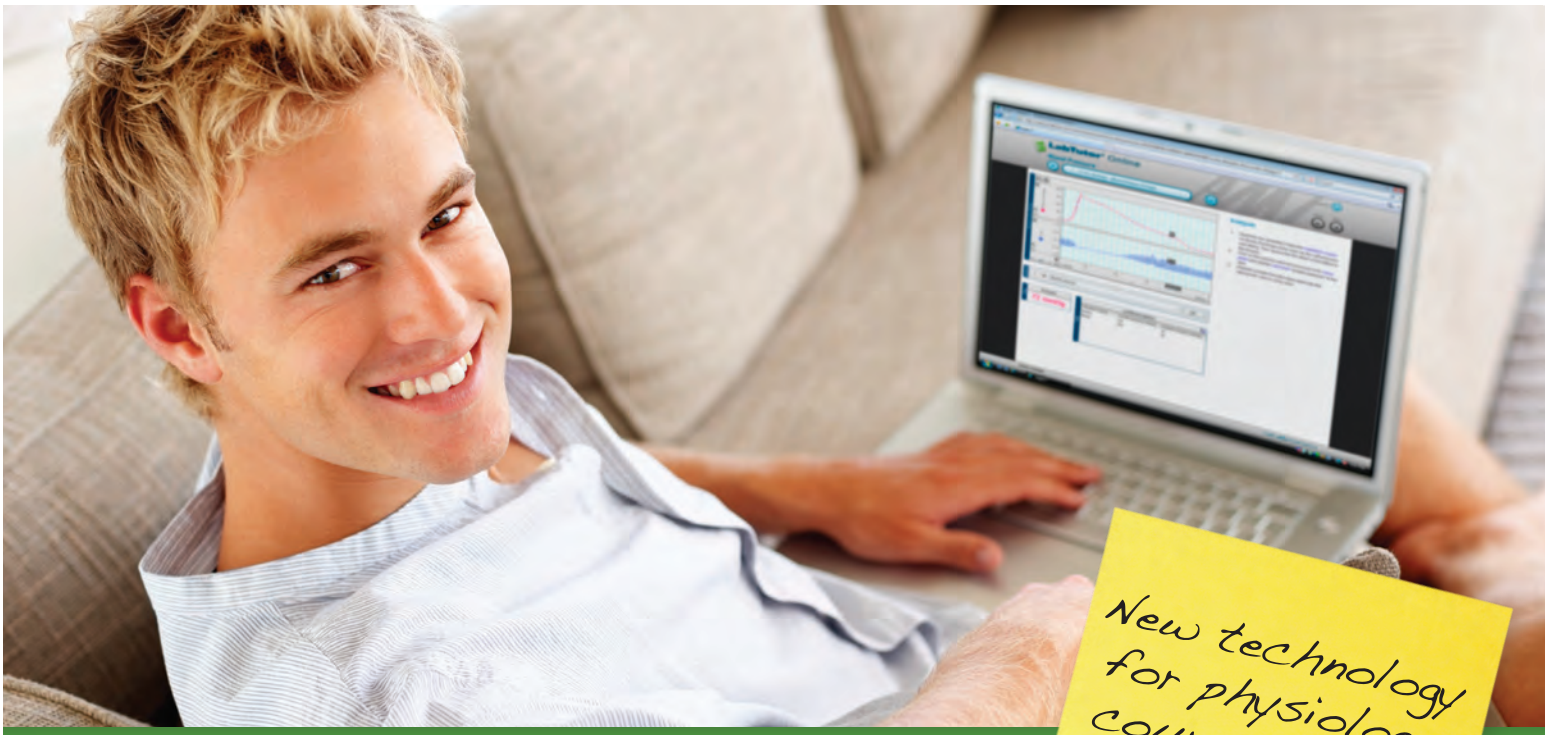
Chance to win a netbook – see Questionnaire on p. 43

Transports of the capillary wall. Charles Michel's exploration of the endothelium

Outreach activities of The Society

How to make a sphincter out of skeletal muscle

50 Years of the Australian Physiological Society



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

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Advancing the science of life

Cover image: Austin Court, a canal-side building in Birmingham city centre.

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Action points

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

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Physiology News

Deadlines
Letters and articles and all other contributions for inclusion in the Autumn 2010 issue, No. 80, should reach the Publications Office (magazine@physoc.org) by **8 July 2010**. Short news items and letters are encouraged, and can usually be included as late copy if space permits.

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

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Guidelines for contributors

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

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

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

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

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

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

In this issue

Welcome to the Summer *Physiology News*.

Summer remains the traditional conference season, and we have half a dozen conference features balanced equally between events yet to take place and those being reported. In particular, one article gives you a preview of Physiology 2010 in Manchester – where I can confidently predict that it *may* not be raining.

Also slightly in the category of 'meetings' is the history of our sister Australian Physiological Society, fifty years old this year (p. 19). Some things about Physiological Societies have changed a bit over the intervening years. In the wonderful 1960 APS meeting photo on p. 20 I counted only one woman, and one member apparently asleep. The picture from the 2010 meeting (p. 22) shows the balance of the sexes now a fair way towards equality. As the 2010 photo is of a conference coffee break I am unable to make a similar fifty-year comparison for sleepers.

We have an enhanced coverage of science policy issues, and science engagement, this time – rather appropriately given the recent UK elections. At a time of global economic downturn it is more important than ever that scientists make the point about the value of science – economic, educational and cultural – not only to opinion-formers, but also direct to the public, young and old. One of the reasons we feature such activities here, Phys Soc-organised or not, is to encourage other Members to *get involved*.

Finally, we are saying thanks and goodbye to two major Society office-holders – outgoing President Clive Orchard (p. 41) and retiring Chief Executive Mike Collis (p. 43). Both have done a tremendous amount for The Society. Clive will now be reverting to his several other important jobs (!), while we wish Mike an enjoyable time investigating French vineyards, among other things.

Austin Elliott
Editor

Who is listening?

One of the constants for scientists worried about the economic and political climate has been the niggling feeling that most politicians do not really 'get' science. This impression has been exacerbated in Britain over the last couple of years by a series of events – perhaps most eye-catchingly by 'Nuttgate', the sacking of the independent drug advisor Prof David Nutt by then Home Secretary Alan Johnson after Nutt aired his views in an invited academic lecture. Another point of contention has been the perceived enthusiasm of politicians, and particularly the former Labour government, for the 'impact agenda' – the idea of judging research, and possibly the disposition of funding, by 'impact', or by likely economic value for particular projects (see Editorial, *PN* **77**). Looming over all has been the spectre of the aforementioned cuts to higher education. Hefty cuts in university funding were announced before the election by the outgoing Labour government, and no-one is betting on that being the last stroke of the axe. Although the research budget was at least notionally protected in the pre-election cutbacks, major cuts to 'capital' projects (in effect, the refurbishment of buildings and laboratories) meant that the renewal of facilities that has occurred in the last decade was already evidently at an end.

Against that backdrop, and with an incoming government with an austerity agenda, the question of how many politicians 'get' science has assumed a new significance. In the run-up to the election, commentators had noted the likely loss from Parliament, either at the polls or due to retirement, of a significant number of experienced and 'science-literate' MPs. These included former chemistry lecturer Brian Iddon (Lab) and former House Science and Technology Committee Chair Phil Willis (LibDem). Last summer also saw molecular biologist and Science Faculty Dean-turned politician Ian Gibson (Lab) depart. There was widespread dismay among scientists on election night when Dr Evan Harris, the Liberal Democrat science spokesman, was narrowly defeated – *Times* science editor Mark Henderson called it 'a terrible night for science'. Harris was perhaps the MP most closely associated with the views of the UK scientific community, having taking a leading role on issues like the impact agenda, Nuttgate, the hybrid embryo bill, the scientific debate-chilling effects of England's libel laws, and the need for assessment of scientific evidence to be central in related policy decisions. A measure of the esteem in which Harris was held can also be gauged from the comment of outgoing Labour science minister Lord Drayson: "Very sad to see Evan Harris lose his seat. He was an outstanding advocate for science and will be sorely missed."

Surveys before the election (for instance [1]) suggest relatively few of the new MPs have backgrounds in science and technology. The scientifically trained MPs that *have* been elected will have big shoes to fill. And computational biologist and newly elected Cambridge MP Julian Huppert (LibDem), as the sole working research scientist in Parliament, seems likely to carry many of the hopes formerly vested in Evan Harris.

The new Minister for Science

Following the election, a reorganisation of Ministerial responsibilities sees universities and science grouped together under Conservative MP David Willetts as Minister. Willetts was perhaps a surprise choice, but he has a long-term interest in both universities and science – see his speech to CaSE a few years ago [2]. He is regarded as a credible potential defender of science, and initial reaction to his appointment was broadly positive.

So far the new Minister has made encouraging noises. For instance, he has stressed both the economic and cultural importance of science; he has said that wider scientific education is clearly good for society; and he has indicated that he feels blue skies research is necessary, and in no way inferior to targeted or applied research. He has also indicated a desire to talk to people from across the UK political spectrum with experience in science organisation and policy, including both Evan Harris and the popular former Labour science minister Lord Sainsbury. In among this, though, were clear signals in Willetts' first interviews and briefings that the science budget will not be specifically protected from the public sector cuts.

Can anything be done about this? There certainly seems to be a chance to mitigate cuts, if scientists speak with a strong and united voice. Science, and universities, traditionally suffer from not being in the public eye in the way that healthcare is – most people are not direct 'consumers' of scientific research, or of tertiary education. However, most scientists are clear that science, and universities, are a key engine of the economy – both in terms of technological advancement, and of training a workforce that is technologically skilled and able to problem-solve. In addition, times of recession typically increase demand for university education; it is not clear how education of increased numbers can be delivered in the face of harsh cuts. In addition to the economic argument, British universities are arguably one of the sectors in which Britain remains globally competitive, with most rankings putting ten to a dozen British universities in the world's top hundred. Put another way, universities are something the UK is good at. Why cut them?

What can we do?

The short answer is 'Write to your MP'. It would be a mistake to think that lobbying by organisations like the Society for Biology and CaSE, or the learned societies, means that individual action is unnecessary. On p. 37 of this issue Mark Downs, the Chief Executive of the Society for Biology, offers several simple messages that scientists should stress to politicians. The first is the central role of science in the economy. The second is the importance of practical as well as theoretical skills in the training of scientists – something which major cuts to university funding for science students will clearly put at risk. And the third is the need to intensify efforts to ensure that scientific evidence is well used and communicated across government. While 'special pleading' – for instance, the claim that some specific scientific disciplines are under special threat – is likely to be of minimal effect, politicians need to know that their constituents care about scientific issues. Some estimates suggest as many as 3 million people in the UK have a training in science and technology. That is a lot of voters.

So as a practical measure, consider writing to your MP to make your views known. Do some research – what is their background and experience? New MPs with a science background will need links in the scientific community, both nationally and locally, to help them to find a role. Non-scientific MPs in constituencies with universities, or with large scientific research establishments, need to hear the voices of people who work there. And tell them that spending on science benefits the economy, and society.

None of this may temper the likely cuts. But one thing is clear: if we do nothing, the effect will be precisely that – nothing.

Austin Elliott

1. http://timesonline.typepad.com/files/sci_spread_5may.htm

2. http://www.sciencecampaign.org.uk/documents/2007/Casenews54p9.pdf

Welcome to The University of Manchester

We extend a warm welcome to everyone attending the Main Meeting in Manchester in July.

When UMIST and the Victoria University of Manchester merged in 2004 to create the largest university in Britain, one early name mooted for the new institution was the 'Manchester United' University! Perhaps unsurprisingly this name was not universally accepted but did at least reflect a brand for which Manchester is globally famous. Sport and music aside, Manchester's more lasting contributions to the world include modern atomic theory (Dalton), discovery of the nucleus (Rutherford), development of the world's first stored-program computer (Kilburn) as well as Alan Turing's seminal work on pattern formation and mathematical biology, which today underpins systems biology. Also, AV Hill spent three very productive years here (1920–23), leaving for UCL just a few months before the Nobel Prize announcement. Hill's most famous discovery from the Manchester era is probably his pioneering work on human muscle performance, including the original idea of 'oxygen debt'.

AV Hill building housing neuroscience.

Physiological research in Manchester

In the current era, Manchester's physiologists are located in new facilities based around three predominant strengths: (i) Cardio-vascular, (ii) Ion channels & signalling and (iii) Neuroscience and these three areas will be represented in the main themes of Manchester 2010 as well as in the preceding YPS meeting.

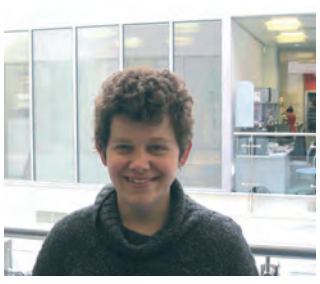
Cardiovascular

Our cardiovascular research is focussed around the laboratories of Mark Boyett (cardiac ion channels), David Eisner (cardiac EC coupling), Arthur Weston (vascular ion channels) and Ludwig Neyses (heart failure pathophysiology) and is spread over two faculties, Life Sciences and the Faculty of Medical & Human Sciences. Cardiovascular Research Fellows include Joy Wang and Katherine Dibb. Andrew Trafford from the group will chair the *Cardiac Damage and Repair* Symposium.

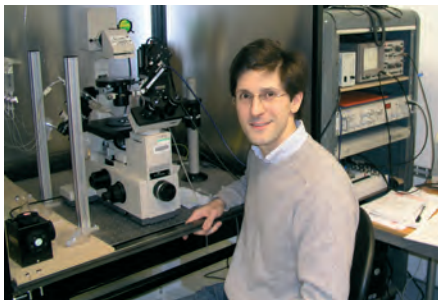
Ion channels, transporters and signalling

Our interests in ion channels, solute transport and molecular sensing & signalling are encompassed in the diverse Channels & Transporters Research group. This includes Maynard Case (epithelial transport), Alison Gurney (pulmonary vascular ion channels), Mark Dunne (pancreatic stem cells) and Alan North (purinoceptors). Donald Ward and Jason Bruce from this group will chair the *Calcium Sensing and Signalling in Health & Disease* symposium while Bob Ford




Top row (from left to right): Maynard Case, Peter Brown and Arthur Weston; Mark Dunne; Alison Gurney. Bottom row: Kath Hinchliffe; David Eisner; Enrico Bracci; and Mark Boyett.


Donald Ward and Jason Bruce; Paolo Tammaro; and Karen Cosgrove.

(membrane biophysics) will chair the *ATP-binding cassette transporters* symposium. Research Fellows from Channels & Transporters include Paolo Tammaro and Karen Cosgrove.

Neurosciences

The neuroscience research group, part of the Neuroscience Research Institute, is based in the new AV Hill building and is focussed around the work of Nancy Rothwell (neuroinflammation), Andrew Loudon (molecular clocks), Rob Lucas (retinal function and circadian clocks), Simon Luckman (appetite and energy regulation), Hugh Piggins (neuropeptides and behaviour) and Alexej Verkhratsky (purinoceptors and calcium imaging). Enrico Bracci will chair the *Striatal Circuits to Basal Ganglia Function* symposium and Nancy Rothwell will deliver this year's Physiological Society Public Lecture. Research Fellows in the Neurosciences group include David Brough, Maria Canal, Curtis Dobson, Natalie Gardiner and Catherine Lawrence.

In addition, Manchester has a strong group of Teaching (and Senior Teaching) Fellows with a physiological focus, who are instrumental in the design and delivery of our physiology teaching to both life science and professional degree students. Accordingly, Teaching Fellows Tracey Speake, Tristan Pocock and Liz Sheader will be contributing a symposium on the *Sustainability of Physiology Teaching & Teachers*.

Finally, in light of our city's sporting connections, we will be holding The Physiological Society dinner at Old Trafford, the home of Manchester United and so we would invite supporters and non-supporters alike to come and join us!

www.physiology2010.org

Donald Ward
Jason Bruce
The University of Manchester

YPS at Manchester

Preceding the Physiology 2010 meeting, Manchester will also play host to a Young Physiologists' Symposium (YPS), organised and run by a group of post-graduate students from the Faculty of Life Sciences at The University of Manchester. The two-day symposium, entitled '*Physiology and disease: advances and perspectives*', will be held from 28–29th June 2010. The meeting will consist of four themed sessions covering the areas of cardiovascular, metabolic, epithelial and neurological disease.

These symposia provide an excellent opportunity for early-career physiologists to present and discuss their work in a relaxed environment. The Society encourages individuals attending the YPS in Manchester to also register for the Main Meeting.

Information about the symposium is available on the website: www.manchester.ac.uk/yps2010

Postgraduate student organisers of this year's YPS meeting.

Coping with hypoxaemia: strategies and solutions

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

There have been major advances in the fields of oxygen sensing, hypoxic sensitivity, physiological response to acute and intermittent hypoxaemia, and adaptations to chronic exposure. Unfortunately, these different issues tend to be aired at specialist meetings and this compartmentalisation tends to limit interaction and cross fertilisation of ideas. This area is of great scientific value due to the possibilities for unravelling basic cellular and integrative mechanisms, and the potential for translation into effective therapies. The meeting has therefore been scheduled to provide a deliberately wide coverage. In order to stimulate exchange of ideas beyond traditional boundaries, and to help promote cross-disciplinary collaborations, the meeting has been designed in a five half-day session split that allows sufficient time for meaningful discussion and networking.

The symposium will provide a broad spectrum of current knowledge on hypoxaemia, presenting an update of this broad area from the molecular and cellular basis of oxygen sensing (emphasising K^+ channels, ROS and HIF), through systems level responses (particularly cerebral and pulmonary circulations) and acute/intermittent hypoxia (e.g. apnoea, training), to the possible limits to adaptive responses in altitude or disease (transcriptional and angiogenic) that may be translated into human performance. Unusually, a comparative aspect has been incorporated into the meeting, allowing lessons from non-model species to inspire alternative avenues of investigation.

The topics covered will be of interest to members of a number of SIGs, including CRAC, human, microvascular, comparative, and cellular signalling. It will be of particular benefit to post-graduate and new post-doctoral attendees in allowing an overview to be presented without conflicting parallel sessions. In addition to the free communications (chosen from submitted general communication abstracts), a point–counterpoint afternoon is planned for early-career scientists to immediately follow the Themed Meeting, to learn about some contentious issues and how conflicting ideas in science may be resolved. Finally, an informal and entertaining talk, including his experience of making physiological measurements on Everest, is planned for after The Society Dinner to be given by Chris Imray.

The venue for the meeting is the IET Birmingham: Austin Court, a unique canal-side listed building located in the city centre. The beautiful restoration has preserved many original features forming its unique historical character – once a metal and nail merchants – and boasts the latest technology, including complimentary Wi-Fi. The majority of rooms have natural daylight with the refreshment room opening out onto Birmingham's canals in Brindleyplace, providing access to numerous amenities and city centre attractions.

Stuart Egginton and George Balanos

Invited Symposium Speakers

Peter Barnes
Imperial College London, UK

Chris Imray
University Hospitals Coventry & Warwickshire, UK

Paul Kemp
Cardiff University, UK

A Mark Evans
University of Edinburgh, UK

Stephen Archer
University of Chicago, USA

Jeremy Ward
King's College London, UK

Teresa Pérez-García
Instituto de Biología y Genética Molecular (IBGM) Valladolid, Spain

Bill Milsom
University of British Columbia, Canada

Tobias Wang
Aarhus University, Denmark

Göran Nilsson
University of Oslo, Norway

Shahrad Taheri
University of Birmingham, UK

Nanduri Prabhakar
University of Chicago, USA

Asif Ahmed
University of Edinburgh, UK

Martin Flück
Manchester Metropolitan University, UK

Andrew Cossins
University of Liverpool, UK

The Peter Stanfield Festschrift

University of Warwick, 12 April 2010

Members of the physiological community probably need no introduction to Peter Stanfield, his enormous and lasting contribution to the K^+ channel field, or indeed his role in The Physiological Society as Secretary, and as an Editor and Reviewing Editor for *The Journal of Physiology*. Although spending most of his illustrious career in Leicester, Peter moved to the University of Warwick in 2001 and retired last autumn. We held a celebratory Symposium at Warwick in his honour. This Symposium featured former members of Peter's lab including his first post-doc, Fran Ashcroft, and later lab members, Ian Forsythe, Caroline Dart and Zoltan Rusznak, as well as collaborators and friends Bertil Hille and Ramon Latorre. Alistair Mathie, another alumnus from Peter's Leicester Department, stepped in at the last minute to replace a speaker who was unfortunately compelled to drop out.

The event was preceded by a celebratory dinner the night before which gathered together the speakers, and various members of Warwick's Neuroscience and Physiology community. This was a chance for old friends to meet again and reminisce and for eager speculation, prompted by Bertil Hille, about what alternative careers Peter might follow in his retirement. Mark Smith, the Pro-Vice Chancellor for Research at Warwick said a few words of welcome and appreciation of Peter's career, and made the point that one indication of someone's standing in the scientific community is the quality of people speaking at the Symposium (clearly outstanding) and how far they had come to be there – with two of the speakers flying over respectively from the northern and southern shores of the Pacific, Peter's reputation spreads far and wide.

The Symposium kicked off with some opening remarks. Blair Grubb (Leicester), now head of Peter's former department, and originally recruited by Peter, gave a moving appreciation of Peter's career and its influence on the ion channel field and particularly the impact that Peter's leadership had at Leicester. This was a theme echoed in many of the comments of subsequent speakers – how influential Peter had been in the development of their own careers and in establishing an environment that allowed them to flourish.

The first speaker was Ian Forsythe, who prefaced his talk with some very amusing comments on the less formal aspects of his life in Peter's lab. These included an admission of boomerang making in the departmental workshop, which eventually culminated in the presentation of a left-handed boomerang to Peter for his birthday. Ian then went on to describe the actions of NO on K^+ currents in the medial nucleus of the trapezoid body (MNTB) neurons. Interestingly, NO acts as a volume transmitter to regulate the functional phenotype of the MNTB cells, greatly enhancing Kv2 in an activity-dependent fashion. Ian provided evidence that this counter-intuitively enhances the fidelity of high-frequency firing of these neurons and hence the fidelity of auditory processing.

Remaining with the brain stem and the auditory system, Zoltan Rusznak from Debrecen, Hungary, talked about his work in the cochlear nucleus. Starting from his earliest work that he had performed with Peter, Zoltan described the Kv channels and their roles in three types of neuron within the dorsal cochlear nucleus. Zoltan explained that the key to understanding function was to be able to unambiguously identify the neurons in the cochlear nucleus through rhodamine and biocytin backfilling with 3D reconstructions providing the most clear-cut method for identification.

The final talk of the lunchtime session was delivered by Bertil Hille. Bertil announced that Peter's next career, given his keen interest in singing, was clearly to become an opera singer. As Peter had attended the whole of Wagner's Ring Cycle in Seattle, Bertil recommended that the role of Wotan was his for the taking. After prescribing this future for Peter, Bertil went on to present a fascinating talk which could be paraphrased by misquoting Bill Clinton: 'It's the lipids, stupid'. The lipid in question is PIP_2 and Bertil showed with an extremely elegant combination of methods how disappearance of PIP_2 underlies G protein inhibition of the KCNQ channel.

The afternoon session started with Alistair Mathie talking about modulation of TASK channels in the cerebellum. This was a particularly germane topic as the latter part

Photos by Roger Thomas

Fran Ashcroft, Peter Stanfield, Phil Langton, Caroline Dart and Blair Grubb.

Bertil Hille answering questions.

of Peter's career has involved investigation of the selectivity filter of TASK channels and indeed Alistair made extensive reference to this work. Alistair initially described the characteristics of the 'standing-outward' K^+ current, or IK_{so}, a leak current important for the maintenance of the membrane potential. Initially, the TASK-1 channel was the favoured candidate to underlie IK_{so}, but surprisingly IK_{so} was still present in TASK-1 knock-out mice. However, Alistair then presented evidence that IK_{so} is carried by a heterodimer of TASK-1 and TASK-3 channels. In TASK-3 knock-out mice, the absence of IK_{so} prevented cerebellar granule cells from firing continuously, which again reinforced the importance of K^+ channels in excitatory communication.

Frances Ashcroft was up next and started with an amusing anecdote about how Peter and Nick Standen set her on her way as an electrophysiologist when she was trying to make recordings from stick insect muscle cells. This led to Peter inviting her to be a post-doc in his lab, and her establishment of the action potential in insect muscle cells being mediated by influx of Ca^{2+} ions. Frances commented on what a wonderful mentor Peter had been and how enjoyable it had been to work with him. She then went on to describe her life-long interest in K^+-ATP channels and her latest work, which characterized mutations in the K^+-ATP channel proteins that are associated with neonatal diabetes. She found that these mutations give a gain of function – the K^+-ATP channel is open under resting conditions – giving rise to the prediction that treatment of such patients with sulphonylurea drugs should be effective at countering this form of diabetes. Amazingly enough, this prediction has been borne out, and this treatment is now being used to revolutionize the lives of many young children – a remarkable and rare story of going from a specific biophysical prediction to effective medical treatment.

After a break for tea, Caroline Dart talked about K^+-ATP channels in smooth muscle cells and their localization to caveolae. Caroline paid tribute not only to Peter but also to his long-time collaborator and friend Nick Standen as an influence on her career. Unfortunately, Nick Standen has been ill for some time and was unable to attend the meeting. Caroline went on to describe localisation of K_{ATP} channel subunits to the caveolae. Furthermore, she also showed that there was a co-localisation of K_{ATP} channel subunits with caveolin and that interaction with caveolin silences K_{ATP} channels, altering their sensitivity to physiological regulators. This provides further insight into the modulation of these versatile K^+ channels.

The final talk was presented by Ramon Latorre. Ramon started by confidently announcing that Bertil Hille was wrong about Peter's future career and that he would provide a revised path for Peter to follow at the end of his talk. He then turned to his structural studies on the Maxi-K channel using the technique LRET (luminescence resonance energy transfer), which has some advantages over the better known FRET for making precise spatial measurements between the donor and acceptor moieties. Application of this technique and combination with voltage clamp allowed Ramon to document the conformational changes of the Maxi-K channel during gating, and he showed some dramatic movements of domains within the channel. Then, Ramon revealed that he had planned a career for Peter as a 'singing cowboy' – drawing on the work of another Peter Stanfield (of the Southampton Institute), who has written a book entitled '*Horse Opera: The Strange History of the 1930s Singing Cowboy*'.

At the end of the meeting Peter was presented with a copy of the textbook on ion channels that he and David Aidley had written that had been signed by all the speakers. Peter then delivered some closing remarks starting with reminiscences of Alan Hodgkin, his PhD supervisor, and moving to the present day and the interests of his grandchildren. This then was a prelude to a final gathering and mingling of speakers and audience over a glass of wine.

The day was highly convivial, the speakers delivered excellent and interesting talks, interspersed with anecdotes about Peter, and it painted a moving picture of Peter not only as a highly distinguished scientist in the K^+ channel field but also as a person. All the speakers had stories that showed how Peter's kindness and support had been influential in their careers. It was also very clear how important the Ion Channel Group founded by Peter Stanfield and Nick Standen had been in the evolution of the field and as a rich, supportive environment to launch the careers of many distinguished alumni. In today's uncertain landscape, this acts as an inspiration to us all.

We thank The Physiological Society for generously supporting this event as well as the Department of Biological Sciences, Warwick Medical School and Neurosolutions Ltd for generously providing additional funds to ensure its success.

Nicholas Dale, Paul Squires, Bruno Frenguelli and Raj Mistry

Towards an understanding of the enteroendocrine system

Metabolism and Endocrinology Themed meeting

The second Metabolism and Endocrinology Themed Meeting, on 24–26 March 2010, was the first meeting of The Physiological Society to be held at the site of a pharmaceutical company. The focused symposium covered the role of the incretin system in the regulation of metabolic and neuronal pathways for appetite control and nutrient handling. There were thirteen invited speakers from UK, Europe and Canada, all leading authorities in their fields of research. In addition, there was a programme of open communications that attracted sixteen oral presentations and thirty-one poster presentations. This number of open communications was a 30% increase on the first of the Metabolism and Endocrinology Themed Meetings. The meeting was organised by Simon Poucher, Alastair Brown and Dave Smith (AstraZeneca Pharmaceuticals) and Fiona Gribble (University of Cambridge) with much help from Rosie Thompson (AstraZeneca Pharmaceuticals) and Sarah Bundock (The Physiological Society) behind the scenes.

A total of 139 registered delegates were welcomed to the meeting by Björn Wallmark, Global Head of Cardiovascular Pre-clinical Research at AstraZeneca Pharmaceuticals. A palpable buzz was already evident during registration and carried on through the lively discussions that followed the oral and poster presentations. Perhaps the excitement was because this was one of very few meetings to cover the incretin area so extensively.

The meeting consisted of five half-day sessions, focused around different aspects of the incretin field. Topics covered included an opening review of the enteroendocrine system, the role of incretins in the therapeutic response to bariatric surgery, how nutrients are sensed in the gut and how the gut microbiome affects whole-body metabolism, reviews of specific enteroendocrine hormones, and the links between physiological challenges, gut peptide responses and signalling to the CNS.

The meeting began with a presentation from Steve Bloom on the potential therapeutic impact of a range of gut peptides upon appetite and body weight. This was followed by talks from Josep Vidal on the effects of gastric bypass upon circulating incretin levels and from Remy Burcelin on the impact of the gut microbiome and its influence on inflammation-mediated metabolic disease. In the afternoon of the first day and the morning of the second, the meeting heard how enterocytes sense glucose (from Soraya Shirazi-Beechey) and lipid sensing in the L-cell (from Pat Brubaker). Fiona Gribble covered how the L cells release incretins following nutrient stimulation. The afternoon session of the second day was dedicated to a review of more specific gut hormones. This was begun by Rachel Batterham, who discussed the role of peptide YY in the regulation of food intake. Peter Flatt covered the role of gastric inhibitory polypeptide (GIP) in the regulation of insulin secretion and metabolism, as well as some potential new roles of GIP in promotion of bone formation and central neuroprotection. Carlos Dieguez reviewed the endocrinology of ghrelin, a peptide secreted from the stomach, and Frank Sundler provided evidence for a potential role of cocaine- and amphetamine-regulated transcript (CART) as a potential incretin.

The final session on the third day had a further three invited presentations. John McLaughlin covered gut peptide responses following inflammatory stimuli in gastro-intestinal disease, whilst Graham Dockray followed this up with a review of how some of the incretins covered during the course of the meeting could signal to the CNS. The meeting was completed by Jens Holst who reviewed how glucagon-like peptide 1 (GLP-1) and GIP responses to food intake were modified by metabolic disease. This was particularly important given the status of GLP-1 mimetics and di-peptidyl peptidase-4 inhibitors for the treatment of type 2 diabetes.

The invited talks were interspersed with free communications, most of which complemented the

theme of the meeting. To provide more opportunity for discussion, presenters of oral communications were also asked to present posters on their area of work. Discussion around the posters was aided by the drinks reception! In a very close contest between the high-quality entries, The Physiological Society Poster Prize was shared by Alicia D'Souza (University of Central Lancashire) for her work on ventricular remodelling in the Goto-Kakizaki rat and Garron Dodd (University of Manchester) for his work on central cannabinoid signalling in the rat. AstraZeneca Pharmaceuticals also awarded a prize for the best oral presentation by an early-career scientist. This was won by Helen Parker (Cambridge Institute of Medical Research) for her work on TGR5-mediated release of GLP-1.

The Society Dinner was held at the Hunting Lodge, Adlington Hall and was hosted by David Tuffin, the UK Head of Cardiovascular Pre-clinical Research at AstraZeneca. Both David and the Meeting Secretary, Prem Kumar, tried to out-do each other as they treated us to a number of humorous stories. Prem thanked not only the organisers of the meeting but also staff from The Physiological Society, Sarah Bundock and David Bennett, who provided invaluable support.

The meeting finished with a Theme business discussion, which highlighted the next Metabolism & Endocrinology Themed Meeting (28 February 2011) and Main Meeting Symposium (31 January 2011) proposal deadlines. Any Member of The Society can, and is encouraged to, propose a potential meeting or symposium. The experience of the current meeting Scientific Organising Committee, was that once the theme and the speakers have been identified The Physiological Society staff do the majority of the organisational work. So don't be shy in coming forward!

Simon Poucher, Alastair Brown, Dave Smith and Fiona Gribble

Towards translational research in motoneurons

Paris, 9–13 July

Motoneurons are the final common output of the central nervous system. Each time motoneurons fire impulses, they induce the contraction of the muscle fibres they innervate in a one-to-one fashion. As muscle action potentials are relatively easy to measure, motoneurons are the only neurons from the central nervous system whose firing pattern can be investigated in human subjects. Since motoneurons receive inputs from many different sensory and descending systems, they represent a window that contains substantial information about both normal and abnormal function for multiple motor systems. Motoneurons are also extensively studied with many approaches (electrophysiology, cellular biology, molecular biology, modelling, etc.) in laboratories using animal models. Although the motor unit is a single functional entity, the study of motor unit firing patterns in humans and the study of motoneuron cellular properties in animal preparations tend to be two separate disciplines, pursued by colleagues with very different training and expertise. For this reason we are organizing an international meeting whose overall goal is to bridge the different approaches for studying motoneurons.

Fifteen sessions will be held during the four and a half days of the meeting. They will cover most of the aspects of research on motoneurons. The first session will be dedicated to the respiratory control of motoneuronal activity. It will be given in honour of Peter Kirkwood, a Member of The Physiological Society. Other sessions will focus on the synaptic and neuromodulatory inputs affecting the excitability of motoneurons, the firing properties of motoneurons in human subjects, the development of motoneurons, the modelling of motoneurons and the history of motoneuron research. Furthermore, several sessions will focus on the plastic changes in motoneurons following stroke, spinal cord injury or peripheral lesions, and also on degeneration of motoneurons during diseases such as amyotrophic lateral sclerosis and spinal muscular atrophy. In order to make the different topics accessible to a broad audience, we will start each day with an introductory review summarizing the state of the art of a given field.

We are strongly encouraging PhD and post-doctoral students to participate actively. They will have the opportunity to show their work during three poster sessions. Each of them will be followed by a discussion.

The meeting will take place at Université Paris Decartes (France) from 9–13 July. For more information, please visit the meeting website: http://motoneuron2010.parisdescartes.fr

CJ Heckman, Didier Orsal, Jean-François Perrier, Daniel Zytnicki

The organizing committee

Joint meeting of the German and Scandinavian Physiological Societies

Copenhagen, 27–30 March 2010

Several of The Society's Members attended the first joint meeting of the German and Scandinavian Physiological Societies in Copenhagen earlier this year. The meeting began on the last Saturday of March with two well-attended sessions, a FEPS young investigator symposium and the Richard Edwards Memorial symposium. This was followed by a highly enjoyable opening ceremony which kicked off with welcoming addresses from the presidents of the host Physiological Societies, followed by the opening plenary lecture delivered by Bengt Saltin (University of Copenhagen) on the mechanisms of muscle hyperaemia. The first day concluded with a welcome reception at the Panum Institute with musical accompaniment provided by the Anders Westfall Jazz Trio. The European flavour of the meeting became apparent here for, whilst UK delegates had all arrived by air, almost all others had made overland journeys. Interest had been added to Christoph Korbmacher's epic drive from Bavaria after a member of his lab from outside the EEC realised that he had forgotten his passport. This necessitated a return to Erlangen and an anxious drive to the north German coast to meet a ferry that was not going to wait. Thankfully the autobahns still have no speed restrictions.

The meeting proper started on Sunday morning, and it quickly became clear that the carefully planned programme covered a broad spectrum of recent physiological research and featured an excellent line-up of invited plenary and symposium speakers from all over the globe. Each morning and afternoon session contained three distinctive elements: a series of parallel symposia consisting of invited presentations 30–35 minutes in length, oral communications sessions with 15 minute talks selected from the submitted abstracts, and a plenary lecture by a speaker of international standing. There were many poster presentations and ample time to view these during

the coffee and lunch breaks. The organisers took great care to include poster presenters in the meeting by giving them all the chance to present their work verbally to a poster review panel which visited every presentation during a designated poster session with wine and beer at the end of each day. The highlights of the first day included the plenary lecture on 'Functions of aquaporins in brain' given by Ole Petter Ottersen (University of Oslo, Norway) and symposia on 'purinergic signalling' and 'pathogenesis of channelopathies'. In the evening, a number of the UK contingent attended a Physiological Society reception and were entertained by

An example of the strange interior decor of Bankerat.

Mike Rennie's stories of his time up north.

The morning of day two began with symposia on a variety of topics including 'molecular mechanisms of synaptic transmission' and 'bicarbonate transport in health and disease'. Before lunch, Richard Warth (University of Regensburg, Germany) gave an interesting plenary lecture on EAST syndrome and mutations in the KCNJ10 potassium channel. For UK delegates, the meetings highlight came on Monday afternoon, when Jenni Harvey (University of Dundee) presented her plenary lecture entitled 'Leptin: food for thought'. This day was rounded off by a lively civic reception at Copenhagen's historic city hall, an impressive building used for ceremonial purposes and state occasions. Amongst many artefacts on display was an impressive gold-plated walrus skull mounted high on the wall.

On the final day of the meeting Helmut Haas (Heinrich-Heine University Düsseldorf, Germany) delivered a fascinating lecture entitled 'Waking with the hypothalamus' and after lunch the meeting came to a close with the final lecture from Walter Boron (Case Western Reserve University, Ohio, USA) on 'pH regulation, bicarbonate transporters'.

All in all it was a very well organised and inspiring meeting and Copenhagen turned out to be an interesting and highly attractive city full of many lively bars and restaurants. Perhaps the most striking of these was Bankerat, a venue which became a popular watering hole for many UK delegates and featured a strange and slightly disturbing décor that included dismembered dolls heads pressed into service as lampshades and stuffed animals arranged into grotesque tableaux.

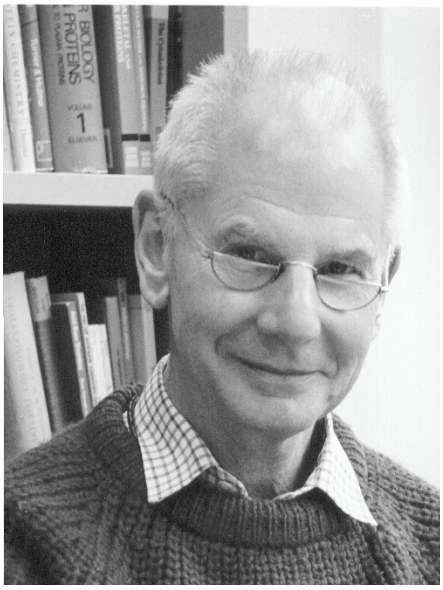
Stuart Wilson and Jenni Harvey
University of Dundee

Starting to work on single capillaries

Much of Charles Michel's research has been concerned with the permeability and exchange properties of the microcirculation. The quantitative techniques developed in his lab for studying the permeability and ultrastructure of single microvessels have advanced our understanding of microvascular permeability and blood–tissue fluid exchange.

Knowing how quickly newly appointed lecturers are expected to demonstrate their research ability today, I feel immensely grateful for the relaxed attitude that I was able to enjoy in the mid-1960s. In January 1966 I became a full-time departmental demonstrator in Physiology at Oxford and a Fellow and Tutor of The Queen's College. My main job was to teach. The College expected me to give tutorials for between 12 and 16 hours a week throughout the three 8 week university terms. In the department my duties involved one to one and a half days per week of practical teaching and, of course, the preparation for these classes. At first I gave only two to four lectures each term but these were to increase. My real prize in the department was a very small laboratory in which I could carry out my own research. Over the previous 2–3 years I had brooded over what experiments I would do when this opportunity arose and I had decided that I would work on microvascular permeability and exchange. So in January 1966, I started to build and acquire equipment. I had no track record of research on the microcirculation that today would be demanded of a young lecturer wishing to set up a research programme. At the time I knew of no other physiologist working on the subject in the UK whom I could consult. As far as I was aware, the only other person who had carried out experiments similar to those I had in mind was EM Landis, and he had just retired from his chair at Harvard to the countryside of New Jersey.

I did have some research experience. Four years earlier under the supervision of Dan Cunningham and Brian Lloyd, I had completed a DPhil on respiratory physiology in Oxford. Dan and Brian had infected me with a very quantitative approach to physiology and set very high standards in the keeping



Charles Michel

of notebooks, analytical work at the bench and in the design of experiments. There had followed an intensive nine month post-doctoral period in New York working with Fred Kao on respiratory regulation in anaesthetised dogs. Here I gained considerable experience in the surgical techniques of mammalian physiology. My time as a research student and post-doc had been intercalated within a medical course and before I set out for New York I promised my father, the Clinical School and my mentors in the Oxford Physiology Laboratory, that I would return for the start of the next academic year to complete my medical studies. So in October 1962 I returned from the US and became a student once again.

Deciding what to do

In 1956 I had entered university to read medicine with the intention of being a clinician but also hoping that someday there might be an opportunity to do research. I became 'hooked' on physiology in my first undergraduate year after reading AV Hill's book '*Living Machinery*' over the Easter vacation. By the time I returned to England from New York, I was certain that I wanted to become an academic physiologist. After three years of research, I was not enthusiastic about being a clinical student, but retrospectively I have always been immensely grateful that I was so strongly encouraged to complete the medical course. I soon became aware of how important physiology is to the rational practice of medicine and how many clinical phenomena raise interesting physiological questions that still remain unanswered. The undergraduate clinical school in Oxford in the early 1960s was very small and with a large regional hospital and a small number of fellow students I had the opportunity of seeing a wide range of clinical cases and gaining considerable practical experience in performing clinical procedures. It was also a time when I was able to think what research I might do as a physiologist with a laboratory of my own.

Although my research had been concerned with respiratory regulation, the interpretation of results often depended on using values in the arterial (or venous) blood to estimate the partial pressure of gases or the concentration of ions in contact with a receptor in the tissue. These calculations were usually based on simple models of microvascular exchange but contained many parameters one really had to guess. I was surprised that so few people were working on microvascular exchange because it seemed to me to be so important to a wide range of physiological problems, from muscular exercise to endocrinology. Also, as I followed my clinical studies, the topic's relevance to clinical medicine and general pathology became very clear indeed. Initially I thought I would tackle some general problems of microvascular exchange using the perfusion techniques that I had learnt in New York. As I tried to understand

the 1951 paper by Pappenheimer, Renkin and Borrero, I came to see the importance of measuring rigorously defined capillary permeability coefficients – something that could be related to the structure of capillary wall. The net exchange of small and large molecules between the blood and the tissues is dependent on microvascular permeability and also on microvascular pressure, flow and the exchange surface area. Whereas permeability is a function of the endothelium, the other microvascular variables are regulated by the smooth muscle of the arterioles and venules. Although ingenuous experiments had been devised to determine the average permeability properties of capillary beds, assumptions were made about the uniformity of permeability and perfusion of the constituent capillaries. Influenced by the way in which the problems of nerve conduction had been clarified by work on single axons and aware of Landis's measurements of pressure and filtration rates in single capillaries, I thought I would try to measure permeability coefficients in single capillaries. From reading papers by Krogh and Landis, it seemed sensible to attempt this on frog mesenteric capillaries. Because there was disagreement between the physiologists' models of microvascular permeability and the interpretation of electron micrographs by morphologists, I hoped that some day it would be possible to combine permeability measurements with ultrastructural studies on the same vessels.

First tentative steps

My first task in 1966 was to acquire and build some equipment. The department gave me £1500 and with this I was able to buy a Wild M5 microscope, an oscilloscope, three Prior micromanipulators and still have a few hundred pounds change. When I was not teaching, I spent much of my daytime in the Department's Mechanical Workshop. Use of the workshop by members of the academic staff was encouraged by 'GL' Sir Lindor Brown (who was Waynflete Professor and Head of Department at the time) and one of the benches was assigned for our use. First I made a Perspex tray to accommodate my frogs and allow me to transilluminate the mesentery. Then, using a design of Simon Miller's, I built a micropipette puller and finally the skeleton of my rig.

With a little practice, it was possible to make preparations of mesenteries of brain-pithed frogs and when these were trans-illuminated and inspected through the M5 microscope, most revealed a spectacularly active microcirculation. To measure the permeability of these microvessels I needed to know the pressure and concentration differences across their walls. After convincing myself that step changes in perfusate concentration in the capillaries could not be achieved by perfusing the mesentery through its artery, I really had to learn to cannulate and perfuse single capillaries.

I knew of only one person, Eugene Landis, who had done this and he had taught himself during evenings and weekends when he was a medical student at the University of Pennsylvania. My admiration for Landis, which was already very high, increased with each attempt I made to follow him. Success eventually came when the Department's Workshop staff made me a micrometer oil drive system, when it became possible to drive the micropipette in an axial direction without touching the Prior manipulator. Just as I was becoming reasonably competent at cannulating and perfusing single capillaries, Rodney Levick arrived in the laboratory as my first research student. Then we made real progress.

Experiments with Evans Blue

I have been remarkably fortunate in the people who have worked with me and never more so than with my first research student. I suggested that we should follow up the report that 'large pores' in capillary walls, whose existence had been proposed to account for the permeation of macromolecules, could be observed as discrete points of leakage of albumin labelled with Evans Blue (T1824). Once Rodney had learned to cannulate and perfuse capillaries, progress was rapid. We were unable to demonstrate 'large pores' in undamaged vessels because the points of leakage were only seen when traces of Evans Blue were present in the perfusate as free dye. To establish this we carried out studies on the binding of Evans Blue to serum albumin and measurements of the diffusion coefficients of both the free dye and the dye–protein complex (Levick & Michel, 1973*a*). Our results, however, did suggest that the microvascular permeability to free dye was reduced in the presence of the dye–protein complex. Since there were reports in the literature that plasma proteins reduced capillary permeability, we decided to investigate this further. Our technique had now improved sufficiently for us to perfuse single vessels with one solution and then remove the micropipette to re-cannulate and re-perfuse with a second solution. Experiments of this type confirmed our earlier impression that the leakage of unbound dye molecules was slowed in the presence of the dye–protein complex. The reduced efflux of dye did not necessarily mean a reduction in capillary permeability because the osmotic pressure of the dye–albumin complex would reduce the fluid filtration rate from the vessel and hence the convective transport of dye. To determine whether this was so, we counterbalanced the osmotic pressure of the albumin in the perfusate by occluding the vessel several hundred micrometres downstream from the micropipette shortly after it had filled with dye and adjusted the pressure applied to the vessel through the micropipette.

We estimated the rate at which the dye crossed a capillary wall from a sequence of timed photographs which were processed as colour slides. To make these estimates more objective, we projected the slides and measured the increase in optical density of the projected image of the tissue immediately surrounding the vessel. The results confirmed that, quite apart from binding with dye molecules to form complexes, albumin reduced the microvascular permeability to the unbound dye (Levick & Michel, 1973*b*).

The success of these experiments gave us several ideas. When the pressure applied to the micropipette exceeded the osmotic pressure of the perfusate, the photographs recorded the increasing concentration of dye–protein complex as fluid was lost from the vessel. Almost to our surprise we found we could calibrate a roll of film from photographs of a range of very dilute solutions of dye in a haemocytometer chamber. Estimates of concentration based on their optical density agreed remarkably well with measurements made on a spectrophotometer. From estimates of the changes in concentration in occluded segments of microvessels, we could estimate the rate of fluid filtration and knowing the capillary pressure, we could then calculate the hydraulic conductivity of the vessel wall (or its hydraulic permeability, L_P). The hydraulic permeability was a true permeability coefficient that was dependent only on the permeability of the capillary wall, i.e. the endothelium.

We realised that if we assumed the interstitial concentration of plasma protein was close to zero and interstitial hydrostatic pressure was close to atmospheric pressure, there were two ways in which we could estimate L_P. First, we could use the changes in fluid filtration immediately before and immediately after a step change in capillary pressure had been applied to the closed-off section vessel (Fig. 1). Second, the rate of fluid filtration through the walls of the vessel at constant pressure should be dependent on the difference between the applied hydrostatic pressure and the osmotic pressure of the plasma proteins of the perfusate if interstitial pressures are small. Because the colloid osmotic pressure of the perfusate within the vessel increased as fluid was filtered from it, the relation between dye concentration and time was exponential, with L_P readily calculable from the rate constant. Estimates of L_P made by these two methods agreed reasonably well and they were also consistent with the classical data of Landis (Levick & Michel, 1977). Whereas Landis's estimate of L_P was based on a population of vessels, this estimate was the L_P of a single vessel.

A special practical class

There was a gap of several months between Rodney Levick resuming his medical course and the appearance of two new research students. Although the methods developed with Rodney were full of promise, measuring changes in optical density from a sequence of colour photographs or even a movie film did not seem to be the way forward. I was thinking of developing a photometer that could be fitted to the microscope or alternatively a method of analysing the signal from a video camera to yield a continuous recording of optical density.

In March 1971, our third year Physiology students could voluntarily spend a few days in a research laboratory for a 'special practical class'. I suggested to the two students who came to my laboratory that we repeated Landis's classical experiment of measuring filtration of fluid in single capillaries of frog mesentery. After several hours of practice, they were able to estimate the rate of fluid filtration per unit area of capillary wall in single capillaries using the Landis's micro-occlusion technique (see Fig. 2*A*). Once they had made a measurement, I cannulated the vessel and measured the pressure within it. The value of fluid filtration rate was plotted against the capillary pressure. Accumulating data for fluid filtration rates in capillaries at different pressures from many vessels (and several frogs) and by plotting corresponding values on a single graph, the students found that despite considerable scatter, a reasonable trend emerged.

After I had made a pressure measurement for one of these points but before I had removed the micropipette from the capillary, I reduced the pressure to draw frog red cells from the microcirculation back to the tip of the micropipette. I then occluded the vessel someway downstream from the micropipette. I could now raise and lower pressure to the closed-off section of vessel and determine the filtration and absorption of fluid from the movements of the red cells and so estimate L_P for that vessel alone (Fig. 2*B*). To avoid conspicuous volume changes in the vessel, the pressure changes had

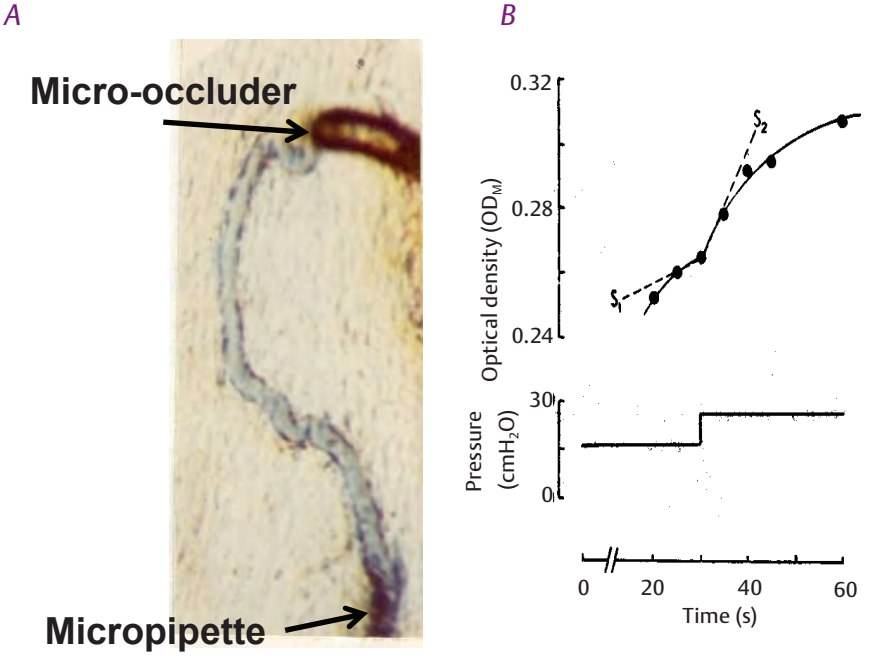


Figure 1. Densitometric method for measuring hydraulic permeability in single capillaries. *A*, photomicrograph of a closed-off section of vessel filled with Evans Blue albumin containing Ringer solution. *B*, measurement of optical density (from which fluid filtration is calculated) before and after a step change in pressure (Levick JR, Oxford DPhil Thesis 1971).

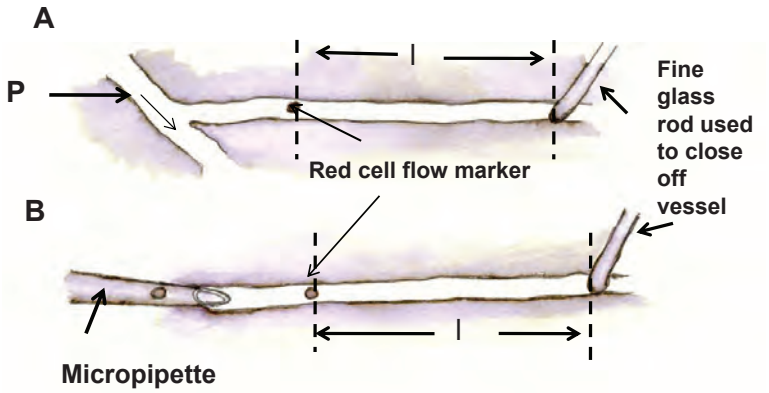


Figure 2. The Landis micro-occlusion technique. Fluid filtration per unit area of vessel wall is estimated from the changes in the length, *l*, of the closed-off cylindrical column of fluid between a marker red cell and the micro-occlusion site. *A*, classical approach used by Landis where after estimating filtration rate, the pressure is measured at *P* in the parent vessel close to the entrance to the occluded section. By this protocol only one pair of values for filtration rate and pressure can usually be made and estimates of L_P involve measurements on many vessels. *B*, microperfusion with a red cell suspension prior to micro-occlusion enables a range of pressures to be applied and estimates of L_P of this section of vessel can be determined.

to be made over the range of 15 to 20 cmH_2O when changes in vessel diameter were not visible. Like the densitometric method, L_p could be estimated both from changes in filtration rate following changes in microvascular pressure and from changes in filtration rate with time at constant pressure. Using the set of data that I had collected during the experiment with the students, the estimates of L_p at constant pressure agreed pretty closely with estimates made on the same capillary from changing the pressure from 18 to 30 cmH_2O. It seemed that this was a more useful technique for the new research students to explore.

The red cell technique for single microvessel L_P

Over the Easter holiday I spent several days making measurements of L_p using the new red cell micro-occlusion technique. Instead of using frog erythrocytes, I filled the micropipette with a suspension of my own red cells and used these as flow markers. Not only were human cells readily available but, being smaller than frog cells, they were less likely to stick at the tip of the micropipette.

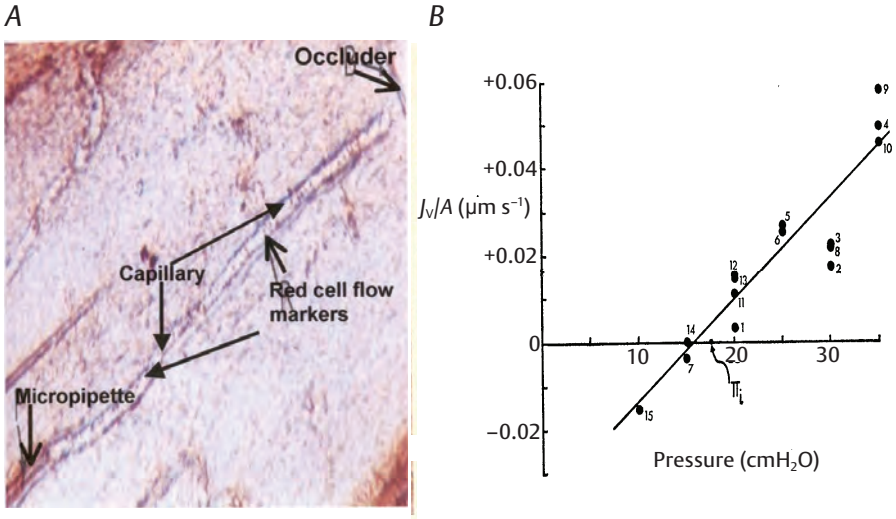


Figure 3. Measurements of L_P in a single vessel. *A*, photomicrograph showing micropipette and micro-occluder as in Fig. 2*B* (Mason JC, Oxford DPhil thesis). *B*, filtration rate per unit area of vessel wall (J_V/A) plotted against capillary pressure for a single vessel; the numbers show the order in which the points were determined and Π_i is the colloid osmotic pressure of the perfusate (Michel *et al*. 1974).

It also meant that composition of the perfusate could be controlled. The two new research students, Juan Mason and John Tooke, were soon improving the technique in many different ways. Within a short time Juan had demonstrated that very low concentrations of serum albumin in the Ringer perfusate would reduce L_P several-fold. John had started to look at the mechanical fragility of frog capillaries and relate this to L_P. They both continued to make rapid progress and while John wrote up his work for an MSc at the end of one year before moving on to complete his medical training, Juan stayed on for a further period to work for a DPhil.

At this time Roy Curry arrived from Monash University as a post-doctoral fellow. He joined in the experiments enthusiastically and soon Juan and he were improving the L_P measurements together (Fig. 3). During conversations over coffee and lunch Juan and Roy recruited the help of Peter Hunter, who was a research student with Derek Bergel at the time, to help with a mathematical model of the changing protein concentration gradients within an occluded section of capillary. Roy improved our rather crude methods for recording the movements of cells initially borrowing the Department's closed circuit TV so that we could record both the movements of the red cells in an occluded vessel and the time. After we had demonstrated the system at the summer meeting of The Physiological Society, a senior Member, aware that our recent application for an equipment grant had been rejected, suggested we applied to a small charity for which he acted as scientific adviser. Within a few months, we had our own CCTV system.

Reaping the benefits

After validating many of the assumptions of the red cell technique for measuring L_P (Michel *et al*. 1974), Juan and Roy completed a comprehensive study of the effects of serum albumin on the L_P (Mason *et al.* 1977). Juan launched into electron microscopy and within a short time was able to inspect micrographs

of capillaries on which he had measured L_P. The technical advance of being able to follow permeability measurements on single capillaries with electron microscopy of the same vessels opened up the possibility of a range of new experiments which would be tackled in our laboratory by Michael Loudon, Geraldine Clough, Roger Adamson and Chris Neal over subsequent years.

We then measured the osmotic reflection coefficients of capillary walls to small hydrophilic solutes. From these experiments we were able to show that approximately 10% of the L_P consisted of a water pathway through the endothelium that was not shared with small solutes (Curry *et al.* 1976). We now recognise this as the aquaporin pathway.

By the mid-1970s we had published several papers on permeability in single capillaries, and grant applications for continuing the research were no longer turned down on the grounds that they were unlikely to bear fruit. Work on single capillaries kept me pleasurably busy for over 30 years and it is good to know that the red cell technique is still being used to measure microvascular permeability. Looking back, I am very grateful to the excellent people who worked with me both then and later and also for the tolerance of 'GL' Brown and David Whitteridge, who as Heads of Oxford Department in the late 1960s and early 1970s, supported me over a six year period that led to few publications and no external funding.

CC Michel

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Letter from Japan 4. A new university

So it has been a while since I sent an update about my post-doctoral research in Japan. This past few months have been very exciting. Okinawa Institute of Science and Technology (OIST) has officially opened. We have moved from the temporary laboratories into our beautiful, shiny new campus and the labs have been put back together. It really is not to be underestimated what a huge job building this new institute has been. The first phase is now complete and we have 'Lab 1' up and running. Moving 25 principal investigators, a few hundred post-docs and a lot of precious laboratory equipment was no mean feat (just look at the photo of the contents of one electrophysiology rig in boxes). Obviously the movers were Japanese so there was also a language barrier which made opening the boxes exciting as the symbols gave no clue as to what was inside them. When I first came to Japan 15 months ago, the new campus was a shell held up by scaffolding. When we came to look around we had to wear hard hats to explore the construction site. As I sit here at my desk and look out at the ocean I think how much has been achieved by OIST in such a short time. The new building really is state-of-the-art. The entrance reminds me of something in a James Bond movie – the car park is surrounded by artificial lakes leading to a tunnel carved through the side of the hill to lead you into the building.

Traditional Okinawan dancers at the opening ceremony.

The rig in boxes.

Nobel Laureate (1981 Nobel Prize in Physiology or Medicine) Torsten Wiesel makes an opening speech to celebrate the Official Opening of OIST.

My boss, Gordon Arbuthnott and I decide on where the equipment will go in our new P2 room.

The official opening ceremony of OIST was spectacular. The sun shone and members of the academic community and Japanese government officials were welcomed with traditional Okinawan dance and song to the new campus. I felt so proud to be involved in such an amazing venture and doubt in my life I will ever be in the same 100 metre radius of so many Nobel prize winners and distinguished academics again.

Life on the new campus is great. In the temporary accommodation, the different research groups were divided across a number of buildings. Now most research groups are in the new campus there is more chance to mingle with the other researchers. We have lots of communal coffee areas where we can discuss work and ideas in a way we couldn't before. I am in the process of re-establishing my electrophysiology rig following the move and am looking forward to being back in the lab. The move gave me some downtime to do analysis and writing which I have really enjoyed.

Fiona Randall

Principal components analysis

Patricia de Winter

In previous articles of this series we have started out with a very large number of measured targets (genes, methylation sites, polymorphisms etc.), which we then reduced to a subset that were statistically different between treatment groups. We then took this subset, which still consisted of a substantial amount of data and used hierarchical clustering to group together profiles that resembled each other. These were visually summarised using a heatmap and dendrograms. Thus far, we still have multidimensional data that exhibit a fairly high degree of variability. In this article we will reduce the dimensionality of these data in order to identify which targets are making the biggest contributions to the variability. One way of doing this is to use principal components analysis (PCA), which was invented by Karl Pearson at the turn of the 20th century. It is a non-parametric analysis, that is, it that can be used irrespective of the type of distribution of the data. This method finds coherent patterns of correlations between variables (targets) to reduce a large number of variables to a small set of factors called components.

An important point is that at this stage we make an assumption that most of the variability in our dataset is due to biological differences and not to other sources such as systematic bias. Systematic biases should have been avoided by good experimental design (such as ensuring that control and experimental samples are not processed as two separate batches), or if unavoidable, removed by the data processing and normalisation techniques that are routinely performed at the microarray facility. There are several unavoidable sources of systematic error and bias: for example, differences in probe labelling efficiency, hybridisation to different slides, processing arrays on different days etc. A very nice illustration of the last two is given in Fig. 2 of Sarkar *et al.* (2009). So for the remainder of this article we will assume that our data are of good quality, the normalisation carried out by the microarray facility has removed systematic biases, and the only sources of variation in the data are biological. We will use a data set from which I have selected seven genes and ten samples to reduce the volume of data and simplify explanations. There are four samples from normal healthy subjects (N) and six from subjects with a disease (D). The analysis would usually be performed on $\log_2$ values, but given the inherent difficulty in understanding data in this format, antilogged data are presented for clarity (Table 1).

Table 1. Raw data for principal components analysis (N, normal; D, disease).

	Gene 1	Gene 2	Gene 3	Gene 4	Gene 5	Gene 6	Gene 7
N1	156	21904	855	1256	298	664	307
N2	247	25063	796	1096	254	754	320
N3	268	20550	723	2427	249	719	245
N4	104	21203	809	2514	265	777	211
D1	472	12967	474	6128	489	4341	601
D2	495	11487	364	7535	571	4150	625
D3	1734	11547	298	4865	554	1699	287
D4	1673	10893	330	4169	628	1905	241
D5	501	11145	287	8245	639	4905	615
D6	1629	11606	307	4634	500	1648	293
Mean	727.8	15836.5	524.3	4286.8	444.7	2156.2	374.5
S.D.	670.6	5606.1	241.3	2495.4	160.8	1666.5	168.4

Table 2. z-scores for the data in Table 1.

	Gene 1	Gene 2	Gene 3	Gene 4	Gene 5	Gene 6	Gene 7
N1	-0.85	1.08	1.37	-1.21	-0.91	-0.90	-0.40
N2	-0.72	1.65	1.13	-1.28	-1.19	-0.84	-0.32
N3	-0.69	0.84	0.82	-0.75	-1.22	-0.86	-0.77
N4	-0.93	0.96	1.18	-0.71	-1.12	-0.83	-0.97
D1	-0.38	-0.51	-0.21	0.74	0.28	1.31	1.35
D2	-0.35	-0.78	-0.66	1.30	0.79	1.20	1.49
D3	1.50	-0.77	-0.94	0.23	0.68	-0.27	-0.52
D4	1.41	-0.88	-0.80	-0.05	1.14	-0.15	-0.79
D5	-0.34	-0.84	-0.98	1.59	1.21	1.65	1.43
D6	1.34	-0.75	-0.90	0.14	0.34	-0.31	-0.49
Mean	0	0	0	0	0	0	0
S.D	1	1	1	1	1	1	1

Even with such a small dataset with many variables (in this case genes) it is difficult to easily discern trends. If we take a closer look, we might see some patterns in the data, for example, some genes such as 2 and 3 seem to have high expression in the normal subjects and lower expression in the disease subjects so these genes may co-vary. You may also have noticed that some genes are much more highly expressed than others, for example, genes 2, 4 and 6. In order to avoid giving undue weight to highly expressed genes, the data are standardised (converted to z-scores). This is done exactly the same way as for hierarchical clustering (see previous issue). The mean value for each gene is subtracted from each observation in that gene profile, and then each difference is divided by the standard deviation for that gene. The mean of each column in this new dataset will be zero with a standard deviation of 1 (Table 2).

We perform pair-wise correlations on all the genes to find out whether any are correlated (Table 3). Genes 2 and 3 are indeed strongly positively correlated, whereas other pairs are strongly negatively correlated, e.g. genes 2 and 5, and some are not correlated at all, e.g. genes 1 and 4. The correlation matrix displays a single number, a correlation coefficient, that

Table 3. Matrix of Pearson's correlation coefficients for the genes in Table 2.

	Gene 1	Gene 2	Gene 3	Gene 4	Gene 5	Gene 6
Gene 2	-0.691					
Gene 3	-0.749	0.968				
Gene 4	0.257	-0.854	-0.826			
Gene 5	0.644	-0.953	-0.947	0.847		
Gene 6	0.025	-0.698	-0.655	0.938	0.737	
Gene 7	-0.230	-0.458	-0.421	0.801	0.514	0.934

Table 4. Eigenanalysis of the correlation matrix in Table 3.

	PC1	PC2	PC3	PC4	PC5	PC6	PC7
Eigenvalue	5.0879	1.7257	0.0810	0.0593	0.0283	0.0134	0.0025
Proportion	0.727	0.247	0.008	0.012	0.004	0.002	0.000
Cumulative	0.727	0.974	0.985	0.994	0.998	1.000	1.000

Table 5. A, coefficients for PC1 and PC2 and **B**, data required to calculate PCA scores for sample N1 (see text for explanation).

A

Variable	PC1	PC2
Gene 1	-0.227	-0.644
Gene 2	0.423	0.191
Gene 3	0.418	0.236
Gene 4	-0.422	0.192
Gene 5	-0.425	-0.145
Gene 6	-0.382	0.378
Gene 7	-0.301	0.540

B

Variable	PC1 coeff	z-score	Product		PC2 coeff	z-score	Product
Gene 1	-0.23	-0.85	0.19		-0.64	-0.85	0.55
Gene 2	0.42	1.08	0.46		0.19	1.08	0.21
Gene 3	0.42	1.37	0.57		0.24	1.37	0.32
Gene 4	-0.42	-1.21	0.51		0.19	-1.21	-0.23
Gene 5	-0.43	-0.91	0.39		-0.15	-0.91	0.13
Gene 6	-0.38	-0.90	0.34		0.38	-0.90	-0.34
Gene 7	-0.30	-0.40	0.12		0.54	-0.40	-0.22
		PC1	**2.59**			PC2	**0.42**

describes a relationship between the expression profiles for each pair of genes. We are on our way to reducing the dimensions of the dataset. The next step is to partition the variability within the dataset by a set of numbers called Eigenvalues. The correlation coefficients in Table 3 can be used as a matrix and the Eigenvalues and PCA outputs are derived from this and from the z-scores in Table 2 using matrix algebra. This is a very complex calculation that requires statistical software – any will do, Minitab, SPSS etc. The objective is to condense the variability of the dataset into a smaller number of numerical descriptors known as principal components.

Let us first take a look at the Eigenvalues, which summarise the biological variability in our data into (in this case) seven principal components (Table 4). The highest Eigenvalue is for principal component 1 (PC1), which accounts for almost 73% of the variability in the data. The proportion is calculated by dividing each Eigenvalue by the number of principal components and can be converted into a percentage by multiplying by 100, so for PC1 5.0879/7 = 0.727, or 72.7%. The second principal component (PC2) accounts for a further 25% of the variability in the data and together these two components account for around 97% of the biological variability. So if we reduce our multidimensional data (seven genes) down to just two principal components, by calculating two scores for each subject they can easily be plotted on a two-dimensional graph and we will capture most of the variability in the dataset.

Statistical software output usually also gives a table of coefficients or 'weights' for each variable, in this case each gene for computation of these scores. Here, I have included only the first two principal components, which are those that are required to produce a graph (Table 5A). We'll start with subject N1. The PC1 coefficient of each gene is multiplied by its corresponding z-score and the products are summed to give a total score for PC1 (Table 5B). This is repeated for PC2. We now have two co-ordinates for subject N1, which is represented as a red data point in Fig. 1. The process is repeated for all other subjects.

In Fig. 1 the normal and disease subjects are widely separated by the first principal component; PC1 represents the variability due to the disease state with a positive value associated with the normal state and a negative value associated with disease state. We can find out which genes contribute most to PC1 (disease state) by looking at Table 5A. We don't have the values for all four normal subjects in this table but as they are all similar we will check those for subject N1. PC1 for the normal subjects is large and positive. The biggest contribution to the PC1 score comes from genes 2, 3 and 4, and for subject N1 the values are 0.46, 0.57, 0.51 and 0.39 (Table 5B). If we go back to the original data we note that genes 2

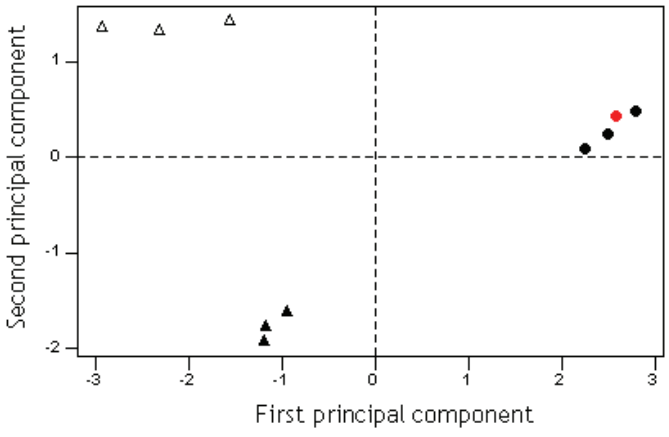

Figure 1. Principal components plot (circles, normal: triangles, disease).

and 3 are downregulated in disease and genes 4 and 5 are upregulated. It is important to note that PC1 does not report the direction of change, only that expression of these genes differs greatly between healthy and disease subjects. The second principal component separates the disease subjects into two groups, three have positive scores (open triangles) and three have negative scores (filled triangles). They both differ from the normal samples, which have scores close to zero. Space limitations proscribe printing the data for all subjects, but analysis has shown that PC2 is concerned with genes involved in differentiation and mainly gene 1 for subjects D3, D4 and D6 who have large positive values of PC2, and genes 6 and 7 for the D1, D2 and D5, who have large negative values of PC2.

So, we started with data for seven genes measured in ten subjects and we have reduced this to two principal components that partition the subjects by disease status and state of differentiation of the cells from which the RNA was extracted. The analysis has also identified how gene expression has changed in groupings within the dataset. It is worth mentioning that, although PCA can be a useful technique, it is sometimes difficult to interpret the meaning of the various components. A recent example from climate change science is the controversy over the so-called 'hockey stick' graph, which illustrates variations of the Earth's surface temperature over the past millenium, showing a sharp increase over the past century. PCA was one of the techniques used to analyse and simplify these very complex data, and has contributed to the continuing debate between climate scientists and climate skeptics over whether recent global temperature variations can be attributed to human activities.

In the next and final article of this series, Peter Cahusac will explain multiple regression in relation to multidimensional data. Suggestions for topics for a second Techniques series are welcome and suggestions can be emailed to: magazine@physoc.org.

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Sarkar *et al*. 2009. Quality assessment and data analysis for microRNA expression arrays. *Nucleic Acids Res* **37**, e17.

The Australian Physiological Society is 50 years old

The Australian Physiological Society (AuPS) recently celebrated the 50th anniversary of its foundation in 1960, 84 years after the foundation of The Physiological Society in 1876. In the 1950s there were just six medical schools in Australia, each, of course, teaching physiology. But physiology was also taught in other places such as veterinary schools and biology departments. Although Sydney was the first university in Australia and had the first Faculty of Medicine, the first medical school was created in the University of Melbourne in 1861, Sydney's School not arriving until 1883. Before World War II Australian universities were underfunded, had small staff numbers and therefore were almost entirely occupied with teaching. Nevertheless, some very good research was being done. For example, in Sydney the Professor of Anatomy, JT Wilson, later Professor of Anatomy in Cambridge, did valuable research in comparative anatomy and embryology, and inspired many students to do research, notably Grafton Elliot Smith and Raymond Dart. These and many other capable students were forced to go abroad because the opportunities for advancement in Australia were so limited. Other talented researchers were Roy (Pansy) Wright and Archie McIntyre.

In the years just before the war physiological research was greatly enhanced by several events. Jack Eccles returned from Oxford in 1937, bringing with him a 'Sherringtonian culture', and assumed the Directorship of the Kanematsu Institute at Sydney Hospital, where he was presently joined by Bernard Katz and Steve Kuffler, refugees from Germany and Austria, respectively. Another important refugee was Rudolph Lemberg, a

Figure 1. Some of the pioneers in the early years of the Australian Physiological Society. Clockwise from top left: Jack Eccles, Archie McIntyre, Peter Bishop and Victor Mcfarlane.

Figure 2. Audience at the Inaugural Meeting of the Australian Physiological Society at the University of Sydney in 1960.

biochemist from Germany, who in 1935 joined the staff of the Kolling Institute at the Royal North Shore Hospital in Sydney. Perhaps the most remarkable arrival was William Feldberg, fresh from his epic collaboration with Henry Dale. In 1936 Feldberg joined CH Kellaway and Macfarlane Burnet at the Walter and Eliza Hall Institute in Melbourne, and although he stayed only two years he produced 10 papers in that time.

In 1943 Eccles went to Otago University in Dunedin, New Zealand and had there the same inspirational effect that he had in Australia. With the creation of the Australian National University in Canberra, Eccles became the Foundation Professor of Physiology in 1952 and thus began what could be called the Golden Age of Australian Neuroscience, which influenced the whole country and indeed the whole world.

During World War II, physiologists worked on problems associated with the performance and welfare of members of the armed forces. Bernard Katz became a radar officer in the Royal Australian Air Force. A notable contribution was made by Frank Cotton, Professor of Physiology in the University of Sydney, who invented and developed an excellent anti-gravity suit for airmen. Howard Florey, an Australian working in England, developed the production of penicillin and came to Australia in 1944 to oversee its manufacture. There were many other examples of war-related research and these made the government realize the importance of physiological research to the health of the nation. As a consequence, when the war ended, much more public money flowed into this area.

The Australian National Health and Medical Research Council had been set up in 1935 but had been starved of funds and had been largely ineffective. After the war it was rejuvenated and since then it has received and disbursed annually increasing funds: it is now the main source of medical research support. Another governmental body, the Australian Research Council, distributes large sums throughout the universities, a significant proportion going to physiology. In 1957 the Federal Government received the Murray Report on universities and adopted most of its recommendations, with the result that there was a massive upgrading of universities and the creation of many new universities. This was a further stimulus to the growth of physiology. A significant factor in the status of physiological research was the creation of the Australian Academy of Science in 1954. The Academy was founded by those Australians who were Fellows of the Royal Society, and was modelled on that Society. One important function of the Academy was to act as the mediating body between Australian physiologists and the international physiological community, especially the International Union of Physiological Sciences (IUPS), on which initially Jack Eccles was the representative. The government itself had gone into research in 1926 with the Council for Scientific and Industrial Research (CSIR), but this did not include physiology until after the war, and then was mainly veterinary. Nowadays there are significant numbers of physiologists in what is now the CSIR Organization (CSIRO).

For all these reasons, the biomedical research field started to expand after the war and the need arose for opportunities to communicate the results of research. A mention should be made about the Australian and New Zealand Association for the Advancement of Science (ANZAAS) which had been created in 1888 on the model of the British Association. Like the BA, its main function was to communicate between scientists and the lay public. At the annual meeting, physiologists presented the results of their research in section N of ANZAAS (physiology, biochemistry, nutrition) in the same way as was done later when the AuPS was formed, but there was always a single lecture to which the public was invited. These meetings were the immediate precursors of the separate physiological society. An example was set by the biochemists with the formation of the Australian Biochemical Society in 1955. Biochemistry split away from physiology just before the war but the ties remain strong and indeed much biochemistry, in the form of molecular biology, is done in physiology departments.

There is no doubt that the driving force in the formation of the Australian Physiological Society was Victor Macfarlane, Professor of Physiology in the University of Queensland. In 1957 he did a tour of the eastern states and secured the support of Peter Bishop in Sydney, Jack Eccles in Canberra, Roy Wright and Frank Shaw in Melbourne, and,

by phone, Bob Whelan in Adelaide and Wilf Simmonds in Perth, for the creation of the Society. In 1958, at the end of the ANZAAS meeting in Adelaide, Eccles chaired a special session to discuss the proposal and there was strong support. There followed lengthy correspondence about the nature of the Society, who should be eligible for membership, and so on. The Society was largely modelled on The Physiological Society, for example in the time allowed for presentation of papers (10 mins) and discussion (5 mins) and in the absence of a president (although this was abandoned in 1981 when Archie McIntyre became the first President). In 1959 WV Macfarlane, who had moved in the meantime to the Australian National University in Canberra, undertook the planning of a scientific meeting to be held in Sydney in May 1960. A draft constitution for the proposed society was drawn up with the assistance of G Sawer.

Eventually the inaugural meeting was held on 26–28 May 1960 in the Physiology Department of the University of Sydney. Macfarlane became the first Secretary and Bishop the first Treasurer. The Physiological Society started with a Dinner (although with no scientific session) so it was appropriate that we also had a Dinner. The cover of the menu was a reproduction of the title page of volume 1 of *The Journal of Physiology* (1878–9) and inside was a copy of a note from Burdon Sanderson proposing a meeting to initiate the formation of The Physiological Society.

There were 126 physiologists and pharmacologists at the inaugural meeting, at which 84 scientific papers were read. A business meeting was held on 26 May, attended by 49 scientists from Australia and New Zealand who were active in the areas of physiology or pharmacology. Those present were invited to consider the form to be taken by the proposed society and to consider the draft constitution. PO Bishop, head of the host department, took the chair and WV Macfarlane acted as secretary. The name of the society chosen at this meeting was the Australian Physiological Society.

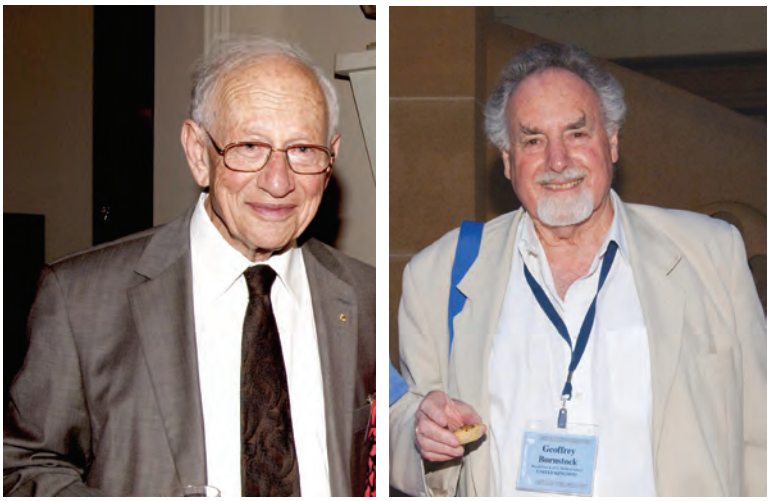

Figure 3. Paul Korner (left) and Geoff Burnstock (right), who attended the 50th Anniversary celebration, also attended the Inaugural Meeting of the Society,

The inaugural meeting appointed the first council, which consisted of eight members with WV Macfarlane as National Secretary and PO Bishop as Treasurer. Subsequent office bearers have been:

National Secretaries

PI Korner, ME Holman, JR Hales, SR O'Donnell, JA Young, TO Morgan, C Bell, AR Luff, RJ Lang, DA Saint and JW Lynch.

Treasurers

MG Taylor, AJ Day, PW Gage, W Burke, C Bell, ALA Boura, DI Cook, CE Hill, DG Allen, CB Neylon and S Bröer.

President

In 1981, the Society created the position of President. The first elected president was AK McIntyre.

Subsequent Presidents

WJ Simmonds, PI Korner, ME Holman, MJ Rand, DR Curtis, JA Young, PW Gage and DJ Adams. DG Allen is the current President.

Since the early 1970s, two scientific meetings a year were held by the Society, hosted by Departments of Physiology or Pharmacology in one or other of the Australian universities. From 1997, due to changing circumstances, in particular the proliferation of specialist societies, the Society moved to hold only one annual meeting. The publication of two issues of the *Proceedings* annually was retained.

In May 1970, the Council felt that the Society was stable enough financially for it to publish its own journal, to be called the *Proceedings of the Australian Physiological and Pharmacological Society*. The first issue, which was produced by an editorial committee consisting of ME Holman, AJ Day and ML Mashford, contained the abstracts of the papers presented at the 10th Annual General Meeting held in the Department of Physiology, University of Melbourne in May 1970. In 1971, DR Curtis was appointed the Editor of the *Proceedings*. Subsequent Editors have been JA Young, JJ Carmody, DF Davey, JM Lingard, AR Luff, LM Aitkin, I McCance and DF Davey (again). In 2002 Council decided to cease publication of paper issues of the *Proceedings*. In 2003, the first on-line submission and publication of the meeting abstracts was undertaken successfully, ensuring that electronic publication will continue in future.

In 1967 the Society became the Australian Physiological and Pharmacological Society even though there was in existence an Australian Society for Clinical and Experimental Pharmacology. Pharmacology was included in the name in recognition of the fact that

Figure 4. Cocktail party held in the courtyard of the Anderson Stuart Building, University of Sydney, 1st February 2010. The Inaugural Meeting of the Australian Physiological Society was held here in May, 1960.

pharmacologists had been strongly represented and very active in the Society from its foundation. The Australasian Society for Clinical and Experimental Pharmacology and Therapeutics drew increasing numbers of pharmacologists away from the Society, leading to the recognition by the early 2000s that the Society had become one representing largely only physiologists. At the Sydney 2003 meeting, a motion was passed to return to the original name, and in February 2004, the Society's name was changed to the 'The Australian Physiological Society Inc.'. However, there has always been an extremely close relationship between physiology and pharmacology, and pharmacological papers have always been acceptable at AuPS meetings. The name of AuPS also did not include any reference to New Zealand although New Zealanders were at the inaugural meeting (and at all subsequent meetings). New Zealand's independence was emphasized by the later creation of the Physiological Society of New Zealand. However, there has always been a warm relationship between Aussies and Kiwis.

One of the reasons for the formation of AuPS was the wish to have an official physiology group that could interact with physiology groups in other countries and with the IUPS. As already mentioned, the Academy performed this role before 1960 but its interaction was necessarily limited. AuPS has always strongly supported the IUPS and other international endeavours. In 1972 it sponsored a Regional Meeting of IUPS (South East Asia and Pacific) at the University of Sydney and in 1983 the 29th Congress of IUPS at the University of New South Wales. AuPS played a key role in the formation of the Federation of Asian and Oceanian Physiological Societies (FAOPS). In 1999 John Young, then President of AuPS, was elected President of FAOPS.

On February 1st 2010, in association with a joint scientific meeting of AuPS and the Australian Neuroscience Society, a seminar and cocktail party was held at the University of Sydney to commemorate the 50th anniversary of the foundation of the Australian Physiological Society, and to acknowledge and celebrate the contributions of the men and women who laid the foundations of Australian physiology and neuroscience. The seminar was chaired by Geoff Burnstock, and the speakers were Paul Korner and Uwe Proske.

With the increase in specialized research fields, accompanied by increasingly specialized technology, it was inevitable that new societies would be formed and that societies covering broad fields of research, such as AuPS, would lose members. AuPS has lost members to specialist societies, such as Neuroscience, Endocrinology and others, but has a stable membership of over 300. In recent years, the Society has held some joint meetings with these other societies, such as the most recent joint meeting with the Australian Neuroscience Society, and has also included multidisciplinary topics in the programs for its scientific meetings.

Over the last 50 years AuPS has provided a forum for the presentation and discussion of research, and in particular has done much to foster the development of post-graduate students and post-doctoral investigators in the early stages of a career in physiology. The Society has contributed greatly to the growth of Australian physiology and will continue to do so for many years to come.

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We are indebted to articles in the *Proceedings of the Australian Physiological and Pharmacological Society*, volumes 9(1) and 14(1), to the article Origins of the Society in the 2006 *Handbook of the Society*, and to the AuPS web site (www.apps.org.au/).

Can you make a sphincter out of skeletal muscle?

An artificial sphincter is one of the holy grails of bioengineering. Theoretical arguments and experimental studies show that the barriers to progress can be overcome.

The need

In conditions such as colorectal cancer, Crohn's disease, ulcerative colitis and inflammatory bowel disease it is frequently necessary to divert the gut, either temporarily or permanently, through a stoma on the abdomen. According to recent estimates, there are approximately 80,000 to 100,000 stoma patients in the UK alone, with 10,000 to 15,000 new stomas created every year. In a high proportion of cases the procedure has a negative impact on quality of life. Patients report leakage, skin rashes, embarrassing noise and odours, interference with sexual activity, and psychological problems arising from the disturbance to body image. Efforts to deal with these problems have met with only isolated success.

What patients need is some way of exerting control over the passage of intestinal contents through the stoma. The biological solution that has been considered for this is an artificial sphincter configured from a body muscle and made to contract and relax by an implanted stimulator. The ideal candidate for this would be the rectus abdominis muscle, which is already used by reconstructive surgeons. The loss of function is well tolerated and, although the donor site is weakened, hernias are rare and can be avoided by applying a reinforcing mesh. This, and the fact that the rectus muscle is well placed for wrapping around the intestine before it emerges through the abdominal wall, makes the surgery entirely feasible. The idea has been around for a number of years (Konsten *et al.* 1993), so why isn't the procedure available?

The wrong kind of muscle?

In the body, the walls of tubular and hollow structures typically contain smooth muscle. This is used to regulate diameter (e.g. blood vessels, branches of the bronchial tree), to propel liquids or solids (e.g. ureter, hepatic duct and intestines) or to expel contents (e.g. urinary bladder, uterus). Smooth muscle is suited to this role for two main reasons:

(a) Its structural organization enables it to contract over a great *range*, as much as 80% (the urinary bladder, for example, can empty completely from an internal volume of 300 ml). As skeletal muscle is sarcomeric, contraction is limited to a maximum of about 25%. Although this type of muscle develops high forces, range of motion must be achieved through the bony levers of the skeleton.

(b) Smooth muscle can maintain tension for long periods with little expenditure of energy. Skeletal muscle will *fatigue* under such conditions.

Rectus abdominis is a skeletal muscle, so isn't any attempt to configure it as a sphincter doomed at the outset?

Hazel Sutherland, Ian Ramnarine, Jonathan Jarvis, Zoe Ashley, Michael Russold and Stanley Salmons (clockwise from top left).

Range of motion: a question of geometry

Consider a sphincter formed by wrapping skeletal muscle around a segment of intestine with the fibres at right-angles to the long axis of the intestine. When the muscle contracts, the radius shortens in the same proportion as the circumference (circumference = 2πr). Thus a fractional shortening Δ in the fibres reduces the radius to $r(1 - \Delta)$. For example, if Δ = 25% and the radius is 7 mm (a realistic intestinal dimension), contraction reduces the radius to 5.25 mm, leaving a patent lumen of 10.5 mm diameter. It appears that a skeletal muscle will never make an effective sphincter. But look again, this time taking account of muscle mechanics.

The muscle wrap has a wall thickness d and an internal radius r_i, corresponding to the external diameter of the intestinal wall, so the external radius r_o is given by:

$$r_o = r_i + d$$

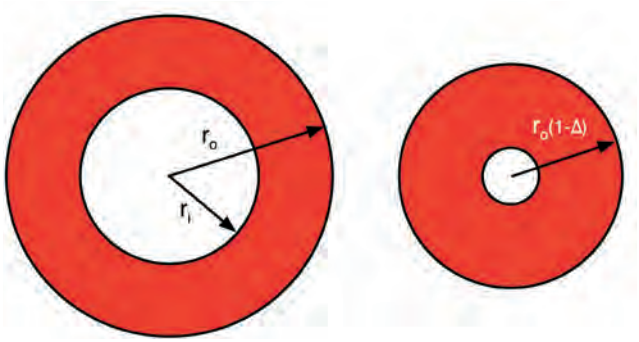

Figure 1. Schematic of sphincter action. The left panel depicts the sphincter in the relaxed state. When the sphincter contracts (right panel) the inner muscle layers are displaced towards the centre.

Thick-walled pressure vessel theory tells us that wall stress is greatest at the inside radius and declines through the thickness of the wall. The outermost muscle fibres of the wrap are therefore the least heavily loaded and, since lightly loaded muscle contracts more quickly, these fibres will shorten more than those adjacent to the gut. During contraction, then, the outer layers of the wrap will displace the bulk of the muscle inwards (Fig. 1).

Muscle volume is proportional to cross-sectional area for a uniform cylindrical wrap. If we equate the cross-sectional areas of an open sphincter and an obliterated (closed) sphincter, we get:

$$\pi\left[r_o^2 - r_i^2\right] = \pi\left[r_o^2(1-\Delta)^2\right]$$

whence

$$\frac{r_o^2}{r_i^2} = \frac{1}{\Delta(2-\Delta)}$$

and since $r_o = r_i + d$

$$\frac{d}{r_i} = \frac{1}{\sqrt{\Delta(2-\Delta)}} - 1 \qquad \text{eqn (1)}$$

Taking the same example of an intestinal diameter of 7 mm and a fractional shortening of 25%, eqn (1) shows that total closure can, in fact, be achieved if the wall thickness is not less than 3.8 mm. In general, for a given fractional shortening, the greater the diameter of the lumen, the thicker the sphincter needed to close it. The thickness of the rectus abdominis muscle is less than 3.8 mm, so for the sphincter to be effective the muscle must be wrapped twice. Theory therefore predicts that the range of contraction need not be an insuperable problem.

Avoiding fatigue

Closing the intestinal lumen in a single contraction is only one step; to maintain continence a sphincter must be capable of maintaining tension for hours. Certainly a body muscle such as rectus abdominis would fatigue under these conditions. There are, however, two tricks that enable even this problem to be overcome.

Skeletal muscles are capable of adapting to a sustained increase in use. The most familiar example of this is the response to endurance exercise – such as the training undertaken by a marathon runner – as a result of which the muscles become more resistant to fatigue. A more profound transformation can be elicited by chronic electrical stimulation (Salmons & Henriksson, 1981; Salmons, 2009). This procedure, often referred to as 'conditioning', activates regulatory phenomena at the gene level which are reflected in muscle physiology, biochemistry and microanatomy at both light and electron microscopic levels (reviewed in Salmons, 2009). In the present context, the relevant features are a slowing of contractile speed and a switch to oxidative metabolic pathways supported by an enhanced blood supply. The latter can be exploited to enhance viability by stimulating the muscle *in situ* before lifting it as a graft (Tang *et al.* 1998).

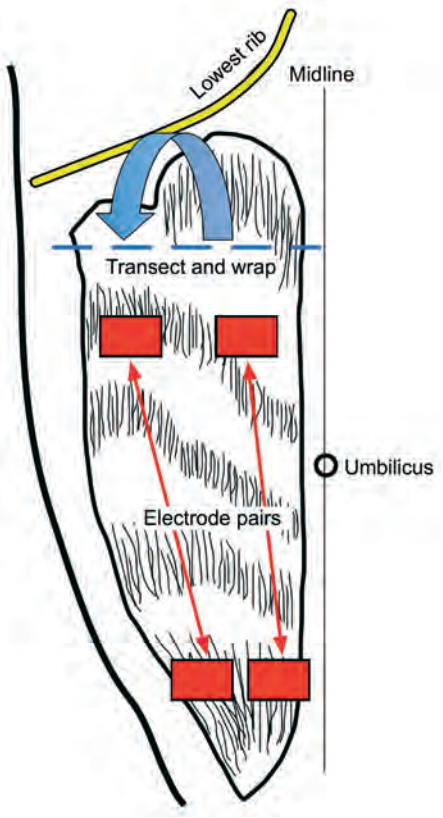

Figure 2. Right rectus abdominis muscle, illustrating how the graft is lifted and wrapped to form a sphincter (blue). The epimyseal electrode pairs (red) divide the muscle functionally into two longitudinal segments.

Thus, a conditioned skeletal muscle graft has properties adapted to continuous use. The metabolic changes allow the muscle to obtain energy continuously from oxygen and nutrients in the blood, and the slow contractile speed enables it to develop adequate force at low frequencies of stimulation, which are less demanding of energy.

There is, however, a problem: the constant, high pressure within the sphincter wall will obstruct the muscle's own blood supply and render it inviable. What can be done about that?

A possible solution would be to interrupt the contraction briefly to allow for reperfusion of the muscle. However, it turns out that even a conditioned muscle relaxes so rapidly that an interruption as brief as 100 ms is enough to lose continence (Russold *et al.* 2010).

Fortunately the forces required are not so large that the whole muscle needs to be recruited at one time. If different segments of the muscle are activated sequentially, closure can be maintained by one segment while blood is flowing back into the adjacent segment (Zonnevijlle *et al*. 2000; Russold *et al.* 2010). The rectus muscle is innervated by several nerves, which are fine and easily damaged. The procedure could be made surgically more robust by using epimysial electrodes but would this provide sufficient separation?

Experimental studies

We started by confirming, on an human cadaver, the practicality of constructing a sphincter from the rectus abdominis muscle. We went on to test the ideas outlined above experimentally. Stimulators were implanted in six pigs and used to precondition the rectus abdominis muscle of one side at 2 Hz continuously (Sutherland *et al*. 2006; Salmons, 2009). The contralateral muscle was used as an unconditioned control. After 4 weeks

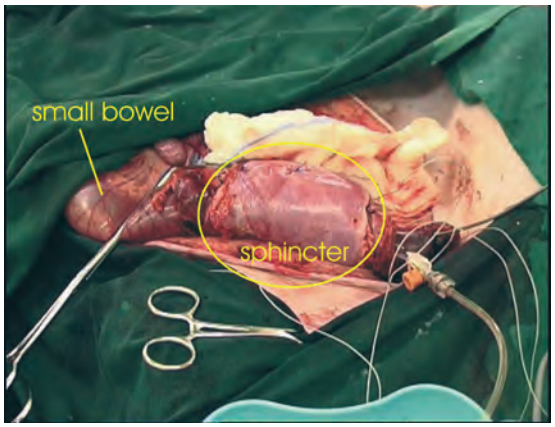

Figure 3. Experimental set-up, illustrating the double-walled sphincter, formed in this case around the small intestine containing saline at a pressure of 50–60 mmHg. The blue dish at lower right was placed to collect leakage; it remained dry as long as stimulation was maintained.

each muscle was mobilized by dividing it at the upper (rostral) end without disturbing the distributed nerves and the blood supply from the inferior epigastric artery (Fig. 2). It was then configured as a sphincter around a segment of intestine and tested for continence against saline at a pressure of 50–60 mmHg (Fig. 3). Stimulating current was directed alternately to longitudinal segments via epimysial electrodes. A full account of the study has been published (Russold *et al.* 2010), but the results were essentially as follows.

The use of epimysial electrodes provided an acceptable degree of separation of the longitudinal segments. By incorporating a slight overlap between the alternating stimulus pulses, we could maintain pressure continuously within the lumen. There was no leakage of pressurized saline with a double wrap, and occlusion of the lumen could be confirmed by ultrasound imaging. However, when the sphincter was configured with a single wrap it was not continent, confirming the theoretical prediction. Conditioning was essential: unconditioned sphincters could not maintain continence, but sphincters created from the preconditioned muscles were still fully continent after 90 min. At this point we were obliged to terminate the experiments, which had already lasted many hours, but there was every indication that the conditioned, double-wrapped sphincter would have continued to be effective for much longer.

Conclusion

This study removes the remaining objections to configuring a sphincter from the rectus abdominis muscle. If the wall thickness of the sphincter is in the proper relationship to its diameter, complete occlusion is possible. Fatigue can be avoided by a combination of preconditioning and segmental stimulation of intramuscular nerve branches. Part of the muscle could be left unstimulated to leave a fast-contracting reserve to resist sudden increases in abdominal pressure due to a cough or sneeze. Use of such a device for even a few hours during the day would enable patients to manage their activities more flexibly.

The goal is therefore achievable. In our experience there is no lack of innovative plastic and reconstructive surgeons. All that is needed is a device manufacturer to make an implantable stimulator that is less complicated than a pacemaker.

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Bless Up

By C R House
AuthorHouse.co.uk
£5.00
ISBN 978-1-4490-8601-5

The suggestion for this book came from House's mentor and friend, Professor Bernard Ginsborg, Its theme is that we are often stamped by the others we meet. And those 'others' are usually unaware of their enduring influence. The title and chapter headings come from the author's life in Grenada and are taken from the rear windows of Grenada's buses. '*Bless Up*' is a Grenadian greeting that opens or closes a conversation. Grenada, however, does not feature further in the memoir which focuses on House's early life in Glasgow where he saw the hardship and humour in ordinary lives and later witnessed internationally renowned scientists at work beyond the limits of his native city.

House was elected a Member of The Physiological Society in 1968 and is the author of Water Transport in Cells and Tissues, a Physiological Society Monograph. He served as an editor of *The Journal of Physiology* and chief editor of *Experimental Physiology*. In 1982 he was elected a Fellow of the Royal Society of Edinburgh and in 2006 an Honorary Member of The Physiological Society.

Chronic micro-inflammation: is it the enemy in the battle for maintaining muscle mass during ageing?

Ageing is characterized by a gradual loss of muscle proteins (sarcopenia), which is ultimately responsible for decreased mobility and autonomy of the elderly. A decreased efficiency of nutrition on skeletal muscle anabolism has been blamed on this deterioration. Containing micro-inflammation that develops during normal ageing may be a good tool to maintain muscle mass and autonomy.

Normal ageing is characterised by a decline in skeletal muscle mass and strength associated with increased muscle fatigability (Fig. 1). This phenomenon, named sarcopenia, reduces physical activity and generates a general weakness in elderly men and women. The weakness of quadriceps muscle predisposes to impaired locomotion, frequent falls and increases the risk of hip fractures in the elderly. In addition, there is an increased susceptibility to illness since skeletal muscles are the major reservoir of body proteins, and consequently of amino acids, which could be used for energy production or the synthesis of acute-phase proteins by the liver. Due to the reduced muscle mass, the ability of aged individuals to fight and recover from stress is impaired. All these factors taken together, sarcopenia reduces the quality of life for the rapidly expanding older population in Western countries. Elucidating the mechanisms that result in muscle wasting in ageing is therefore of obvious importance. It is estimated that $20–30 billion of health costs are spent in the USA on problems directly related to sarcopenia (Schneider & Guralnik, 1990).

Alterations in mechanical and biochemical properties of skeletal muscle are very similar in elderly men and women, and elderly rodents. Muscle proteins undergo a continuous process of degradation and synthesis. Thus, protein storage in skeletal muscle results directly from the overall balance between the rates of protein synthesis and breakdown. Sarcopenia observed during ageing is then the consequence of a decreased protein synthesis, increased proteolysis or a combination of the two phenomena.

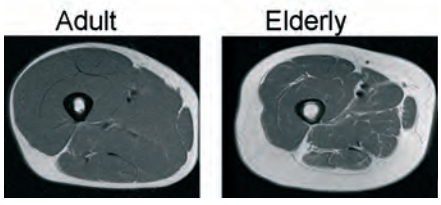

Figure 1. Leg skeletal muscle in adult and elderly humans.

Dominique Dardevet (left) and Laurent Mosoni.

Ageing and postprandial muscle protein metabolism

Throughout the day, these activities of protein synthesis and breakdown are not stable and vary according to the nutritional state: whole body proteins are stored after food intake and lost after prolonged period without food (e.g. at night). On a short-term basis in adult, muscle protein mass remains stable and fasting muscle protein loss is compensated by the same protein gain during the feeding period (Fig. 2). These changes are mediated by feeding-induced increases in plasma concentrations of both nutrients and hormones. Many studies suggest that amino acids and insulin play major roles in promoting postprandial protein anabolism. In rats, Mosoni *et al*. (1995) and Dardevet *et al*. (2002) found that protein synthesis was stimulated by feeding only in adult but not in elderly rats. This loss of protein synthesis response to the anabolic effect of food intake could be involved in age-related muscle protein loss, since every day fasting-induced protein loss will not be completely recovered during the postprandial period in the oldest subjects. Several studies have indicated that branched-chain amino acids (BCAA: leucine, valine and isoleucine) regulate skeletal muscle protein synthesis and proteolysis. A decrease in muscle protein synthesis and proteolysis sensitivity to leucine during ageing may explain the defect in postprandial anabolism (Combaret *et al*. 2005; Katsanos *et al*. 2006; Rieu *et al*. 2006). The decreased sensitivity of postprandial muscle protein metabolism to leucine in the elderly suggests that the signalling pathway that carries the leucine signal to the protein translation machinery is less responsive to the amino acid than in adults (Dardevet *et al*. 2000). Increasing dietary intake of leucine has been shown to present beneficial effects on skeletal muscle postprandial anabolism in the elderly (reviewed in Balage *et al*. 2010).

Sarcopenia and low-grade inflammation

The origin of this resistance to the stimulatory effect of food intake (i.e. dietary amino acid leucine) is unknown and still under question. Ageing may be also characterized by the development of a low-grade inflammatory state. Levels of inflammatory markers, such as interleukin-6 (IL6) and C reactive protein (CRP), increase slightly with ageing, and these higher levels are correlated with disability and mortality in humans. Even if the increase is moderate, higher levels of cytokines and CRP increase the risk of muscle strength loss (Schaap *et al*. 2006) and are correlated with lower muscle mass in healthy older persons. Cytokines and particularly tumour necrosis factor-α impair skeletal muscle protein synthesis by decreasing the stimulation of the mTOR signalling pathways. Interestingly, this pathway has been shown to be responsible for muscle protein synthesis stimulation by food intake and amino acids. Therefore, a modulation of low-grade inflammation during ageing may be beneficial to improve the response of muscle protein metabolism to

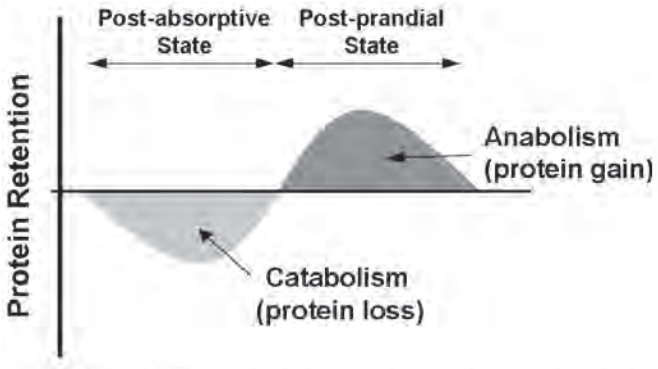

Figure 2. Theoretical changes in nitrogen balance during the post-absorptive and postprandial states.

food intake. To test this hypothesis, a non-steroidal anti-inflammatory drug (NSAID) which inhibits cyclooxygenase activities, including COX2, was used (Ibuprofen). It significantly increased fed state muscle protein synthesis by 25% and significantly decreased proteolysis in a rat model (Fig. 3). The restoration of muscle protein anabolism during the postprandial state by controlling the development of low-grade inflammation significantly decreased sarcopenia (Rieu *et al*. 2009).

Interestingly, an antioxidant supplementation has been shown to reduce the inflammation state and/or oxidative stress in the elderly and has also been shown to improve the ability of leucine to stimulate protein synthesis in muscles of old rats independently of an increase in leucine availability (Marzani *et al*. 2008).

Conclusion

Our recent observations have identified low-grade inflammation as an important target for pharmacological, nutritional and lifestyle interventions that aim to limit sarcopenia and muscle weakness in the rapidly growing elderly population.

In order to slow down the loss of muscle proteins during ageing, it is necessary to take into account the higher threshold for the stimulation of muscle protein anabolism. It is possible that eating more protein/amino acids/leucine will enable older individuals to reach the plasma amino acid concentration corresponding to this higher threshold. It also seems possible that pharmacological (ibuprofen), nutritional (fruits and vegetables) or lifestyle (exercise) interventions that reduce low-grade inflammation, could lower the threshold for protein metabolism in the elderly (Fig. 4).

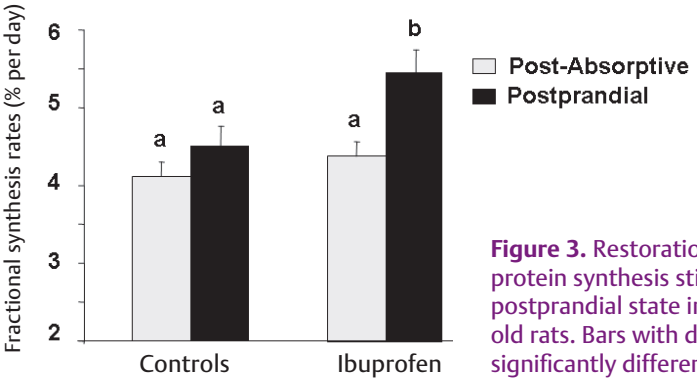

Figure 3. Restoration of muscle protein synthesis stimulation at the postprandial state in ibuprofen-treated old rats. Bars with different letters are significantly different.

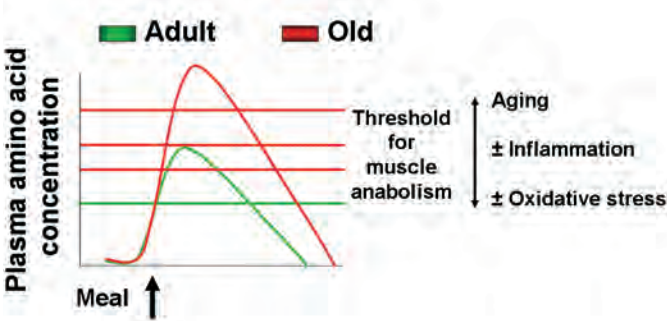

Figure 4. Increased threshold for muscle protein stimulation during ageing. This increase is modulated (±) by the presence (↑) or absence (↓) in inflammation and oxidative stress.

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Analyses of motor unit firing patterns and synchrony contribute to our understanding of tremor mechanisms in Parkinson's disease

Muscle force tremors and neurogenic components of tremors of body segments reflect rhythms in motor unit activities. The analysis of motor unit firing in Parkinson's disease discloses the characteristics of the synchrony and discharge patterns underlying tremor, and also furnishes estimates of their impacts on the tremor amplitude. It further reveals features of the neural input provided by the tremor generator to motoneuron populations.

After decades of research, the mechanisms of rest and postural tremor representing common signs of Parkinson's disease (PD) remain uncertain. There is ample evidence implicating supraspinal centres (basal ganglia, thalamus) and strong neural synchrony in the generation of the tremor rhythm. Observations involving spinal/peripheral action in tremor genesis also exist. An overview of such findings has been presented by Christakos *et al*. (2009).

Tremor investigations in PD have so far focused on cerebral activities, yet the neurogenic components of rest and postural tremor result from muscle force tremors caused by rhythmical motor unit (MU) activities. Furthermore, MU populations represent sites of convergence of various central and peripheral neural influences. Thus, the firing synchrony and patterns of MUs, apart from being responsible for the tremor formation and properties, also carry information on the neural input provided by the tremor generator to motoneuron (MN) populations.

In a recent study (Christakos *et al*. 2009), we recorded force tremor and simultaneous MU spikes from a finger muscle contracting against a force transducer in 19 parkinsonian subjects and 19 age-matched control subjects.

We analysed the MU firing synchrony using a combination of coherence and cross-correlation computations on MU–tremor pairs (Christakos, 1997). This technique, being experimentally and computationally efficient, is particularly suitable in cases of patients with movement disorders. We also studied the MU firing patterns using higher-order interspike interval (ISI) analysis,




From top left clockwise: Constantinos Christakos, Dimitri Anastasopoulos, Evangelos Anagnostou and Sophia Erimaki.

which is an appropriate technique in cases of complex rhythmical firing. We then considered the observed characteristics of MU firing in relation to both the tremor properties and the features of the neural input to the MUs.

Rhythmical firing synchrony within the active motor unit population

In the two minute records from our patients there were epochs (Fig. 1) where MUs exhibited rhythmical spike doublets and triplets at the tremor frequency (observed range 4.5–8.0 Hz). The mean ISIs within such spike-events were of the order of 50 ms. These epochs were randomly interchanged with epochs showing the normal rhythmical firing at the MUs' individual discharge rates. Spike doublets were first studied by Dietz *et al*. (1974) and Dengler *et al*. (1989) who also described an association with overt tremor.

In *all* epochs of the patients' records, *all* 50 studied MUs, irrespective of their discharge rates, exhibited a firing component that was coherent to the tremor (Fig. 1). Moreover, the synchronous MU components were in-phase, according to the MU–tremor cross-correlograms which indicated a clear tendency for MU spikes to occur around the tremor minima. A widespread and in-phase tremor-related synchrony was also present in the control subjects, as it is in younger normal adults (Christakos *et al*. 2006).

The strength of the tremor-related synchrony ranged from very small to very large in the patients' contractions, as it did in those of the control subjects. In terms of MU–tremor coherence, the observed range in both groups was 0.10 to 0.90, where 1.0 is the maximal coherence value for perfect linear correlation. However, this coherence was on average significantly higher in the patients' group (0.50 *vs*. 0.36).

Firing patterns of motor units

The other clear difference to the control group was that the synchronous MU components partly represented rhythmical sequences of spike events (doublets/triplets). This behaviour has important consequences for parkinsonian tremor.

Specifically, the tremor amplitude in the 2 minute records of the patients was much larger than that in the control subjects. As seen in Fig. 2, both amplitudes increased with increasing MU–tremor coherence, but, throughout, their ratio was around 3.0. Further, the observed coherence difference between the two groups (0.14) could only account in small part for this ratio. Therefore, the large tremor of the patients is primarily due to the rhythmical spike doublets and triplets.

The study of this phenomenon therefore presents particular interest. Higher-order ISI analysis (Fig. 1) enabled us to quantify the incidences of doublets/triplets and to arrive at the following simple rule: for MUs firing above the tremor frequency, all spikes in excess participate in the formation of doublets; there are thus doublets in all tremor cycles when the MU rate is twice the tremor frequency; similarly, for MUs firing at even higher rates, up to three times the tremor frequency, there are triplets interchanged with doublets.

In both the patients and the control subjects, no MU was found to fire below the tremor frequency, i.e. the MU recruitment rate coincided with the latter frequency (see also Erimaki & Christakos, 2008). Given the size principle governing the recruitment and rate coding of MUs, the doublets/triplets were therefore exhibited by medium-sized and small MUs. The numerous such MUs contribute rhythmical sequences of twitch doublets/triplets, i.e. large force pulses, to the tremor, thus causing its enhancement.

Neural input to motoneuron populations

The observed characteristics of the tremor-related synchrony (widespread, in-phase) are consistent with the concept of a common rhythmical input provided by the tremor generator to the MN population. According to the observed rule regarding the incidences of doublets/triplets, MUs firing at high mean rates exhibit, in response to this synaptic input, a slower imposed rhythm of spike events.

As we previously discussed (Christakos *et al*. 2009), the other observed characteristic, namely, the fairly fixed (*ca*. 50 ms) mean ISIs within doublets/triplets, probably manifests features of this rhythmical synaptic input. Accordingly, the

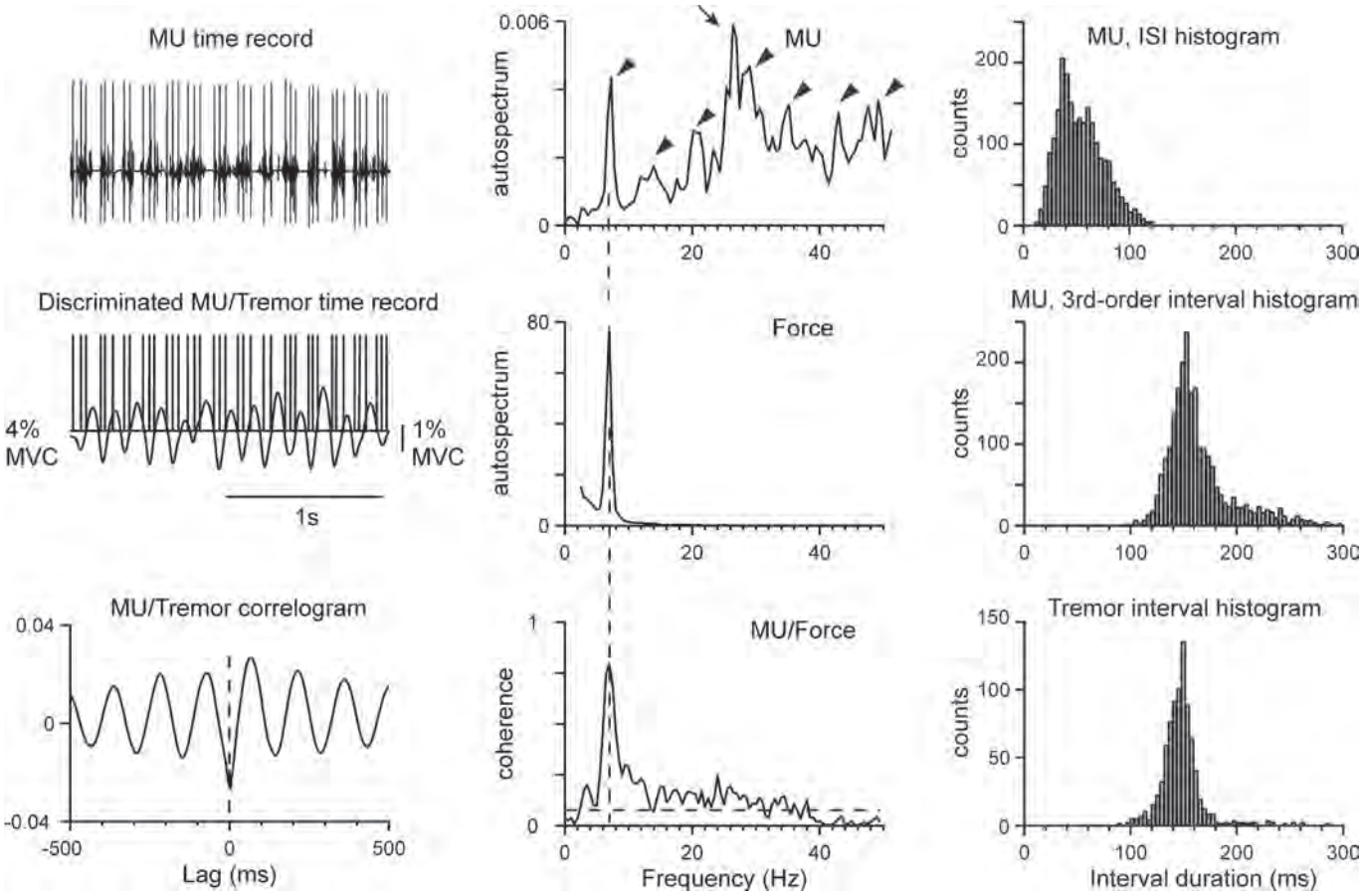

Figure 1. Tremor-related motor unit firing in epochs exhibiting doublets and triplets. Left column: the record of discriminated MU spikes (mean rate near 20 Hz) shows rhythmical triplets interchanged with doublets, that all occur around the minima of the tremor oscillation. This rhythmical locking is verified by the central trough at zero lag in the oscillatory cross-correlogram. Middle column: the MU autospectrum shows a large component, and also harmonic ones (arrowheads), representing the rhythmical doublets/triplets. This component has the same frequency (*ca*. 7 Hz) as the dominant component manifesting the tremor in the force autospectrum. The high MU/tremor coherence (0.82) indicates rhythmical correlations of this MU to other MUs in the active population, and thus reveals the presence of rhythmical population synchrony. Notably, the peak near 25 Hz (arrow) reflects the ISIs within triplets. Right column: the ISI histogram exhibits a clear peak around 40 ms, manifesting the short ISIs within doublets/triplets, and smaller local peaks around 60 and 100 ms manifesting the longer ISIs following such spike events. The third-order intervals representing sums of three consequtive ISIs are manifested in the respective histogram as a single peak around 145 ms which coincides with the mean tremor interval. This peak indicates that quite often two short ISIs and a longer one combined so as to form one tremor period, and allows the estimation of the incidence of triplets.

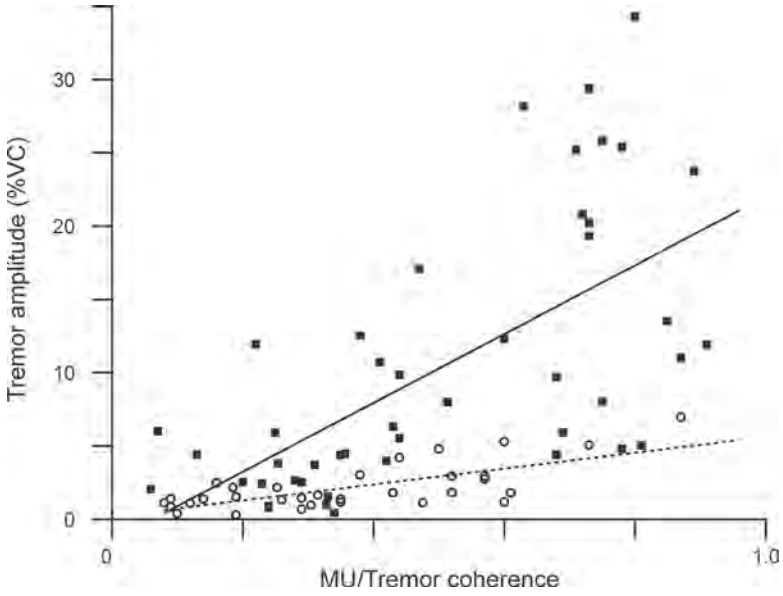

Figure 2. Dependence of the tremor amplitude on the strength of the synchrony. Patients: filled squares, continuous line; control subjects: open circles, dashed line. The scatter diagrams for both groups show an increase in tremor amplitude as the MU/tremor coherence increases. However, the slope of the best-fit straight line is much steeper for the patients group, whereby the tremor of the patients is about three times larger than that of the control subjects.

tremor-related input may exhibit multiple bursts per cycle, separated by *ca*. 50 ms; alternatively, it may have an additional 20 Hz component, such as the 11–30 Hz components that exist in movement-related neural activities. These possibilities could therefore facilitate the exploration of the neural generator of parkinsonian force tremor.

Postural tremor which involves voluntary muscle contractions, but also rest tremor, is known to be largely neurogenic. The observed MU behaviours are therefore relevant for such parkinsonian tremors. More generally, analyses of MU firing synchrony and patterns could facilitate the study of tremors in other movement disorders.

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'Seaweed 'key to tackling' obesity'
'Are some of us born to be fat?'

As a PhD student focusing on the molecular mechanisms behind obesity, few days go by without a headline catching my eye. The stories which follow these bold claims have varying degrees of accuracy, a far cry from the peer-reviewed articles we are used to reading. When I saw an advert in *Physiology News* for a science and media workshop, run by Sense about Science, it sounded like a perfect opportunity to understand more about the somewhat tentative relationship scientists have with those who control what the public read.

The workshop, held at Manchester University, was friendly, fun and most definitely useful. It centred around two panel sessions: the first involved three scientists who had experience with the media; the second had journalists ranging from a BBC radio reporter to a writer for the *Daily Mail*. I found both sessions really informative and encouraging.

The scientists gave good hints on working with the media, rather than against. Some of the key points they made included researching any journalists who may contact you and ensuring you discuss how you will be cited. We were also reminded that it is important to liaise with press officers, as they have vast experience of working with the media. All in all it was a positive session and encouraged me to consider media interaction as beneficial rather than detrimental.

In the afternoon session we got the opposite perspective and began to understand the mind of a journalist. As you'd predict, we scientists were a little hesitant and somewhat confrontational at first but as time passed we began to realise journalists do want to report accurate science. A recurring theme that stuck with me was the need to have human impact in a story. Even if a substantial break-through is made in an animal model without a discussion on how it may impact on humans, even in several years, no media will be interested. On the surface this is quite annoying to a PhD student spending endless hours determining the activity of a single enzyme in a specific tissue of an animal model. However, when it comes to a quick flick through a newspaper, I read the stories with attractive headlines whether reporting science, religion or politics. The second point that really stuck in my mind, at least in the case of newspapers, is that the headlines are not written by the journalist writing the story; in fact, the final say on all content comes from the editor. This means even a journalist with the best intentions to report accurate science can find the impact and angle of their story vastly altered at the last minute.

I've already highlighted how interesting and useful the panel sessions were, but the day didn't stop there. I learnt a little more about Sense about Science, which I hadn't heard of before this workshop. They are a charity which responds to scientific misrepresentation in public discussion; personally I like to think of them as the middle man between scientists and civic groups needing factual and accurate scientific advice. They also developed the Voice of Young Science programme (VoYS), which gives young scientists the chance to get involved in public debates and react to concerns in scientific reports. They have put together a range of very useful literature which can help to guide young (and indeed 'mature') scientists through speaking to the media and getting involved in standing up for science (www.senseaboutscience.org.uk).

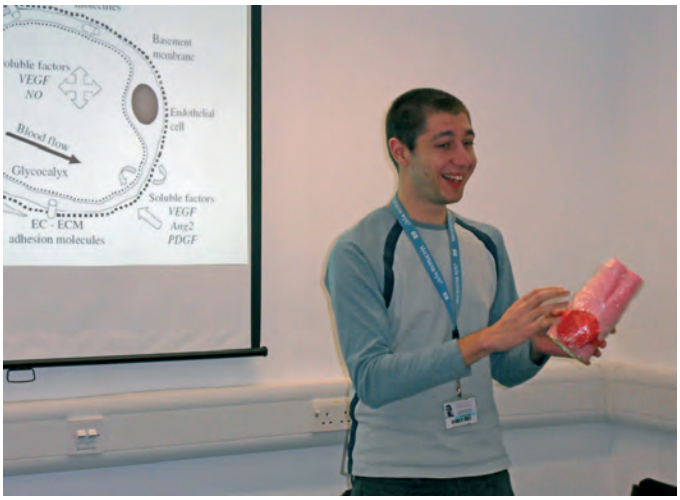
The workshop taught me a lot and definitely opened my eyes to the perspective of those working in the media. It also gave me the chance to interact with other young scientists and discover how they are promoting science to the public.

At this point in my career I'm not about to generate a media frenzy but I certainly feel I'm more informed about how I could get my research into the public domain. I think any public interaction is a great way to get rid of the 'geeky scientist' stereotype and encourage people to take note of science in the media. Overall the session helped us realise the best way to stop getting annoyed by reports of 'bad science' is to get out there and spread the word.

Rachel Dakin
The University of Edinburgh

Members of The Physiology Society have priority places on these workshops. For further information about Voice of Young Science (VoYS) and future workshops please visit the website (www.senseaboutscience.org/VoYS) or contact Julia Wilson at jwilson@senseaboutscience.org

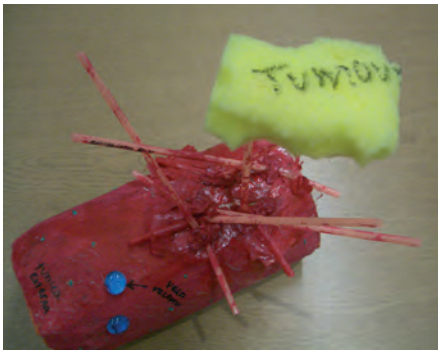
Birmingham's next top (angiogenesis) model



Creating from scratch a three-dimensional model of angiogenesis (blood vessel growth from existing vessels, best known for its role in cancers) isn't just a fun thing to do for a couple of hours on a wet Wednesday. For one thing, it takes a lot longer than a couple of hours to build one. It also requires forethought, planning, creativity and knowledge of the subject. In addition to all that, the first year medical students who had chosen my first attempts at running an SSC (student selected component) had to endure listening and discussing the subject with me before separating into pairs and researching a particular aspect of angiogenesis they themselves had chosen to study.

As a junior post-doctoral researcher studying the role of platelets in differing forms of physiological angiogenesis with Stuart Egginton, Roy Bicknell and Steve Watson at the University of Birmingham's College of Medical and Dental Sciences, and somebody with an interest in spreading the word about angiogenesis, I jumped at the chance to put forward an SSC proposal. I wanted to do more than simply lecture the students or have them write presentations, so eventually I fell upon the idea of Birmingham's next top (angiogenesis) model, which I thought would appeal to the students. It carried risk, and some colleagues I spoke to about it weren't convinced I could pull it off, since it required the students to get into the spirit of the SSC and, dare I say it, enjoy themselves. However, when I asked the students why they had chosen that particular SSC, they said almost without exception that it was because the SSC sounded the most interesting, and demonstrated a level of creativity not offered by others.

Tomorrow's Doctors is the document in which the General Medical Council describes the educational requirements for medical students. They require a minimum of 25% (up to 33%) of the curriculum to be spent in a series of SSCs, allowing students to study more deeply subjects of interest to them. The aim is to provide a broader education than the core curriculum, and one which helps develop skills in self-directed learning, confidence in various fields including presentation skills, and the consideration of potential career paths (such as becoming an angiogenesis researcher, for instance). Angiogenesis isn't taught as part of the core curriculum, and it therefore seemed perfect for an SSC, given its importance in physiological homeostasis as well as disease progression.



Models (top to bottom): tumour angiogenesis, endothelial sprout growth and longitudinal splitting/shear-induced angiogenesis.

At the last session, during which the students presented their models to the rest of the group, I overheard a number of the students saying how much they had enjoyed the week and making the models. This was clear from the quality of their verbal communications describing the models they had created, and from the answers given to questions (which came predominantly from the group themselves). I was surprised by the intricacy and care put into each and every model presented that day – models that demonstrated the skills I have described earlier. I think this shows that given a little thought about the style of discussion sessions such as tutorials, students aren't those silent droids which fail to make eye contact. I very much enjoyed the experience, and I know from feedback that the students felt the same way. Perhaps as a final gesture, they offered their models to me, which now sit on my office window, for everyone that passes by to understand the differing forms of physiological angiogenesis.

Ian M Packham
University of Birmingham

'You can't ring fence a vacuum'

Officially the title of this cross-party debate, organised by the Campaign for Science and Engineering (CaSE) and which I attended on 13th January at The Institution of Engineering and Technology in London, was 'Making Science and Engineering Policy an Election Issue'. I prefer my alternative, though, which was a remark made during the event. The speakers were Science and Innovation Minister Lord Drayson, his Conservative shadow (opposite number) Adam Afriyie, and Dr Evan Harris, former medic and Science Spokesman for the Liberal Democrats. By the time this issue reaches readers, the next UK government will have been elected. The size of UK science's slice of the pie will depend on who wins, judging from the discussion.

Chaired by Roger Highfield, Editor of the *New Scientist*, the debate was in 'BBC *Question Time*' format, meaning that the questions were not pre-disclosed to the speakers. The debate took place before any party manifestos were published; however, at the time of writing this report they were available online, so I have the advantage of being able to compare what was said with what has now been committed to paper.

The elephant in the room was that thorny issue for science – it is *not* a vote winner. This is because science is not a core issue that bothers the general public. Matters that directly affect people – the Health Service, schools, taxes – are their main concerns. So does science have any hope at all of cutting much ice with politicians? Are they forward-thinking enough to realise that the bases upon which our comfortable modern lives have been constructed result mainly from innovations in science, engineering, and – yes – technology? More pertinently, perhaps, are they sufficiently convinced of this to put their money where their mouth is?

Ah yes. Money – or funding, if you prefer – inevitably the first and biggest question. When asked by Jade Juniper of AstraZeneca how committed the panel were to investing in the science base for the future, Adam Afriyie stated there was 'no doubt' that science, engineering and design underpin economic growth and that the UK economy has been far too biased towards financial services. He avoided the issue of the Conservative party's commitment to funding, though, by emphasising instead that what was more important is 'that it doesn't fluctuate from year to year.' Hmmm. Personally, speaking as a jobbing research scientist, I would like the cash up front, please. Lots of it.

Lord Drayson dwelt upon Labour's record in office of increasing science funding. But we want to know about the *future*, Paul – not just the past. The best Drayson could come up with looking forward is that we will all have to tighten our belts. That'll be cuts then. But to be fair, he is probably constrained by Party policy and the wishes of the Treasury.

Evan Harris responded by saying that the question should be what the Parties *will* be doing, not what individuals – like science spokesmen – who are already committed to science, would *like* to do. He had the audience eating out of his hand with the quip 'If Labour politicians were like Lord Drayson, or indeed [Lord] David Sainsbury, rather than...I don't know ... Alan Johnson, Jackie Smith, or any home secretary, then I wouldn't feel so strongly [against] what Paul's party stands for.' He continued that it would be important to consult the manifestos when they come out to see what those say about each Party's commitment to science. Good idea Evan – I will do just that at the end of this piece.

Martin Barstow from the University of Leicester asked why, during the current economic climate, Britain had not implemented a stimulus package. Lord Drayson replied that Labour had done so, but had chosen to do it via specific mechanisms such as investing in the Technology

Campaign for Science and Engineering in the UK

Strategy Board, which has gone into projects at the applied end of science. Not quite Barack Obama's $750bn economic stimulus package, one would have to say.

Luke Alfie of OxiTech and the University of Oxford asked what impact and outcomes the panel expected from government-funded research in universities. Lord Drayson's answer was impressively philosophical:

'It's to understand better the world... we are in, it's to answer some of the most important questions about who we are and where... we come from. It is to help us live in a better way, to answer some of the greater challenges which we face as a human race... and within that it is also important that it makes a major contribution to improvement in our wellbeing and our economic growth.'

Evan Harris did not disagree, but commented on Labour's initiative to assess retrospectively researchers' 'impact' as part of allocating future funding. He stated that the Liberal Democrats would remove this requirement 'to make people jump through hoops on impact', arguing that Labour's initiative would force people to make things up, or deter them from going down a path where they cannot make a convincing story. Adam Afriyie stated that spending a few minutes thinking about the impact of one's research is a useful exercise, but that the decision to fund should be based on the quality of the research proposal and not on the anticipated or projected outcomes. I like the latter half of that answer.

Moving on to education, Sir John Holman of the National Science Learning Centre wanted to know what were the key educational policies for ensuring a strong science base for the UK. Evan

Harris would like to ensure that priority places in universities are filled, and to say to universities that autonomy does *not* mean the freedom to spend our money as if education is an unconstrained market by filling places in subjects that are demand-led (a hint of antipathy towards media studies was detectable here!). He would also like to reduce the burden of debt for graduates, as it's clearly less of a distorting factor on career choice.

Adam Afriyie took a different tack. He thinks that some of the sexiest careers in the world are in science. Hmmm – sexy? You know, the scientists and engineers that make those quite sexy iPhones and PDAs. Ah, *those*. Well, Adam, I suspect many physiologists rather think that 'traditional' science, as you termed it, is important too. But at least Afriyie's party will repay the student loan of any graduate who goes into teaching. The Labour education policy, echoing previous elections, is to deliver a greater proportion of young people studying science and taking science further through their education – I read that as widening participation.

Andrea Marchessetti of the International Policy Network wanted to know what the panel thought was the relationship between private and public funding of science. Lord Drayson thought that the two should work together as effectively as possible so that they reinforce each other, because 'we have to ensure that we provide the incentives for industry to maintain investment in science.' Evan Harris stated that there is an issue with general departmental funding of science outside the ringfence that he would like to see addressed; he was not convinced that Labour's R&D tax credits are necessarily the best way forward. Adam Afriyie eulogised about the UK's fantastic basic research, but pointed out that we have been sliding down the world economic forum tables of competitiveness. He thinks that this means there is an innovation gap where our research is not being translated into the high-tech products, services, jobs and economic growth that the country requires.

On the issue of how the next government could support and encourage charitable donations for medical research, raised by Tracy Loftis of Cancer Research UK, both the Labour and Conservative speakers replied that we should encourage people to give to charities. Handy policy, that – if one is feeling cynical, it means that government is relieved of part of its responsibility. I suspect Tracy Loftis was probably after some sort of commitment to allow medical charities to be exempt from any sort of tax (for example, refunding to the charity income tax paid by its employees). Evan Harris proposed a cracking solution: 'I would urge the Labour party to say to Bernie Ecclestone, and the Conservative party to Zac Goldsmith, don't give your money to the political party – give it to these cancer charities.'

'Nutt-gate' – the sacking of independent drug advisor Prof David Nutt by Home Secretary Alan Johnson – came up, as did the lack of scientific expertise in any future parliament. Alice Henchley of the Royal Society wanted to know if the speakers were concerned. Evan Harris was more concerned about a lack of understanding of the scientific method and of peer review (which is not, he said, 'a government minister getting a baroness to cast her eye over a press release'). Adam Afriyie has won his campaign to ensure that every incoming Tory MP will have compulsory science induction lessons, which is laudable, though the thought of it made me giggle. And Paul Drayson has ensured that under Labour the Science Minister is in the Cabinet.

The shock of the evening came with the discussion on the Nutt affair, when Adam Afriyie stated that he thought that 'It is right...that any Minister and any Secretary of State, if they have an adviser, should be able to dismiss them on any terms at all... even if they just don't like them.' The audience were incredulous, and Drayson visibly and audibly gasped. Evan Harris retaliated with a question: what if George Bush had sacked every environmental climate change adviser until he got one that agreed with him? Would that be right? But Adam remained... adamant.

Finally, the Chair took a question from Sile Lane from Sense about Science about what the Parties will do with respect to the effects of the UK's libel laws on scientific freedom of speech. Both Labour and Conservative speakers thought the current laws untenable. As Evan Harris chairs the cross-party campaign for libel law reform he has been working closely with Sile on this issue. He specified that we need to ensure that the defence that exists for responsible journalism is clear, and probably statutory, and that peer review (which, he said, is more responsible than even the most responsible journalists) should be an automatic defence of 'Qualified Privilege'. As he recognised a few journalists in the audience, he quipped that peer review would slow them down a bit!

Patricia de Winter
University College London

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The delay of the electrical response of nerve to a second stimulus

Francis Gotch (1910)

J Physiol **40**, 250–274

Many readers have probably experienced, as student, teacher or both, the classical isolated frog sciatic nerve experiment, with its demonstration of, *inter alia*, compound action potentials, nerve thresholds, conduction velocity, and absolute and relative refractory periods. Less may know that the basic experimental set-up is well over a century old. The demonstration of compound action potentials and the refractory period – performed using the frog sciatic nerve – are probably the best known work of Francis Gotch (1853–1913).

Gotch is remembered as a pioneer of electrophysiology – he also recorded the earliest electroretinograms – and as assistant, protégé and ultimately successor to his mentor John Burdon Sanderson (1828–1905). Gotch discovered refractory periods in 1899, eleven years before the present paper, which uses essentially the same technique and apparatus as the earlier work.

For the physiologists of the late 19th and early 20th century, measuring small time-dependent electrical signals was a major technical challenge. There were none of the oscilloscopes and fast voltmeters that appeared in labs by the late 1930s and 1940s, let alone the PC-based systems of today. The only suitable instrument available was the capillary electrometer, invented in 1875.

The capillary electrometer (or Lippmann electrometer after its inventor) converted changes in 'electromotive force' (EMF) – potential difference or voltage – into a more-or-less instantaneous change in the level of a very narrow mercury column in a capillary tube. If a bright light was placed so as to project the image of the mercury level onto a photographic plate or film, and the plate or film was moved past the light at a known rate, a time course of the change in EMF/voltage could be produced. Burdon Sanderson and Gotch's electrometer used an arc source as the light, and moved the detection film with a kind of model railway system. Improved and refined with the help of the physicist George Burch, it represented the state of the art for its time. Nonetheless, as John Henderson puts it with dry understatement in his biography of another user of the electrometer, Ernest Starling: "As can be imagined, the capillary electrometer was a very cumbersome creature".

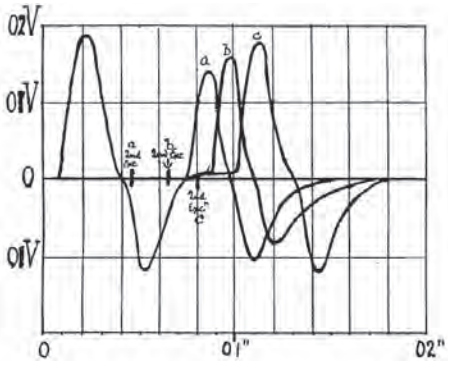
Gotch and Burch's (1899) demonstration of the existence of the refractory period concluded with these words:

"The very numerous records which we now possess of the electrical responses in nerve as evoked by one or by two stimuli furnish data for the determination of the development and subsidence of the electromotive force of such responses under a large variety of conditions. For such determinations a very large number of analyses... are desirable. We hope at an early date to give in detail the results of these analyses... We confidently expect that the analyses will throw light upon the question as to how far the possibility of evoking a second electrical response is related to a definite phase in the subsidence of a previous electromotive effect [action potential], and upon the wider question as to whether under any circumstances a summation of successive excitatory electromotive changes in nerve is a possibility."

'At an early date' was rather optimistic, for it was not until 1910 that Gotch returned to the subject of paired stimuli. He tells us "I possess a large number of records obtained, with the cooperation of G. J. Burch, by photographing the movements of my sensitive electrometer... These have now been re-examined and carefully analysed."

The 1910 paper concentrates on whether the response (i.e. the compound nerve action potential) to a second stimulus is delayed (has a greater latency) than the response to a first stimulus a few milliseconds earlier. What mainly stands out in the paper for me are the beautiful experimental records, redrawn from the photographs Gotch refers to. Figure 4 of the paper, showing clearly the smaller compound action potentials elicited during the relative refractory period (due, as we now know, to the failure of the second stimulus to exceed the temporarily raised thresholds of many nerve axons), is essentially identical to the traces one would see on a storage oscilloscope or PC screen today. For me it serves as a fitting tribute to the ingenuity and perseverance of the workers of a century and more ago.

Biographical information on Francis Gotch is surprisingly sparse. Though an FRS, he was not accorded an obituary in the Royal Society journals, and only a fairly short one in the *BMJ*. He was born in Bristol, the son of a Baptist Minister, and later attended University College London. Burdon Sanderson became Jodrell Professor of Physiology at UCL



Three electrical responses to paired stimuli in a frog sciatic nerve at 8°C; Fig 4 from Gotch (1910).

in 1874. In an obituary of his mentor, Gotch writes of coming "as a student... under the sway of [Burdon Sanderson's] inspiring personality".

Gotch became Burdon Sanderson's main assistant at UCL, and in the early 1880s followed him to Oxford. He stayed there for the remainder of his career save for four years (1891–1895) as the first Holt Professor of Physiology in Liverpool (he was succeeded there by Charles Sherrington, also later to replace Gotch in Oxford after his death). Gotch was elected FRS in 1891 and Waynflete Professor of Physiology in 1895.

Gotch married Rosamund Horsley, daughter of a family of noted musicians and artists, and younger sister of the pioneering neurosurgeon (and physiologist) Sir Victor Horsley (1857–1916). The chronology strongly suggests Gotch met Victor Horsley first, either when both were students at UCL or later via The Physiological Society (both men first appear in The Society minute books in 1882–3). The two later collaborated on several important studies of the nervous system. Gotch presumably met his future wife through her brother.

Gotch lived only three more years after the publication of the 1910 paper, dying unexpectedly in the summer of 1913 aged only 60. His *BMJ* obituarist, Prof Arthur Thomson, describes him as a man of great patience and charm: "Of manner mostly serious, Gotch had a subtle sense of humour which oftentimes enlivened a social evening. Catholic in his tastes in art and literature, he had a musician's appreciation of music and a sportsman's fondness for games."

Austin Elliott

Gotch F & Burch GJ (1899). The electrical response of nerve to two stimuli. *J Physiol* **24**, 410–426.

Thomson A (1913). Francis Gotch. *BMJ* **2**, 209.

A simple, elegant paleoecologically derived solution to the problems of career advancement during a recession

"*In a pond without fish, the shrimp shall be king*" 8th century Chinese proverb.

After a couple of drinks, a range of solutions to a looming career crisis keep popping into my mind. I am a scientist employed on a research grant, the cash is running out and cuts of anything up to £900 million in science research funding are coming. Even my usually jocular head of department admitted "Times are hard. 2010 and 11 are going to be difficult years".

I can see one thing looming. Unemployment!

In a lightly inebriated state, I have considered four career survival options.

Lie and make your research appear biomedical or translational. A difficult one this as everybody else is doing it.

A career change. A difficult proposition when there are 2.5 million unemployed.

Sleep with my head of department. Even for the sexually ambivalent this is deeply dodgy in our litigation-sensitive age. Anyway, I am very bald and I think my head of department prefers blondes, but I am not entirely sure which gender.

And the 'paleoecologically derived solution'. I stumbled on this whilst reading about the Permian period. "When dominance of a particular ecological niche passes from one group of organisms to another, it is rarely because the group is 'superior' to the old and usually occurs because a mass extinction event eliminates the old dominant group and makes way for the new".

I was initially confused by the relevance of this paleontological curate's egg to funding and career advancement but after a third drink, it became clear. During the Permian period, terrestrial ecosystems were run as a cartel by mammal like reptiles. Meanwhile, their insignificant dinosaur-like cousins, suppressed, marginalised, destined to a brief footnote in evolutionary history, lurked in the undergrowth. During the late Permian mass extinction, a runaway greenhouse effect wiped out 80% of life on earth. For dinosaurs this was equivalent to winning the lottery because it wiped out the competition and left a whole range of temporally vacated ecosystems that could be exploited. The rest is history. Dinosaurs terrorised land ecosystems for 200 million years (don't you just love it when the underdogs finally get to go on the rampage; personally I would settle for a 20 year reign of terror as that takes me through to retirement age). Then at the end of the Cretaceous period, an asteroid wiped out the dinosaurs but, for a hitherto obscure homeothermic nocturnal offshoot of the mammal-like reptiles, it was an apocalyptically derived Christmas present, empty ecosystems, ripe for exploitation.

If you are an obscure and under-appreciated junior scientist lurking in the academic undergrowth you are probably wondering, what have 'mass extinctions' got to do with career advancement? You first need to ask what '*ecological niche*' or scientific discipline do I work in and what '*organisms*' dominate my scientific niche. Most are dominated by 10 scientists – they squander 90% of the funds, decide what projects get funding, what papers get published, who gets appointed and where.

If you were to engineer a little accidental 'mass scientific extinction' that befell all 10, your static career prospects could be transformed. One minor academic apocalypse and your scientific field could be opened up like a evolutionarily depleted post-Permian vista – a 90% increase in available funding in your field with nobody left alive to apply for it (other than you), no hostile comments on your grant or fellowship applications and nobody left alive who really has a clue about what they are talking about when you apply for a range of fellowships or permanent posts.

Quite frankly it's no use bumping off the occasional scientific competitor who has bruised your ego. Your aim needs to be 'the termination of an entire scientific clade'. However, one minor caveat to this approach is that mass homicide is a marginally illegal activity in most western countries and therefore balancing the egocentric satisfaction obtained from the elimination of a vast swathe of potential scientific competitors, whilst simultaneously avoiding the attentions of the criminal justice system, would require careful planning.

There are a number of films that might be of help in transforming any fantasies generated by your perfectly sane and rational ego into a practical homicidal-based career development plan. One I particularly enjoyed (but please keep this between ourselves) was the classic horror film '*Theatre of Blood*' where a deranged Shakespearian actor (wonderfully played by Vincent Price) takes poetic but extremely grisly revenge on a number of theatrical critics who denied him recognition, killing them one by one using methods inspired by Shakespearian plays.

Dr Keith Cormorant

PS. Surprisingly, *Theatre of Blood* (1973), directed by Douglas Hickox and starring Vincent Price, is not normally shown at career development symposiums.

Science funding – the need for common purpose

Mark Downs

Whatever flavour of new Government emerges from the general election one thing is certain: they will not be over-endowed with scientific expertise. Partly as a fall-out from the expenses scandal, the number of parliamentarians standing down at the election is significant. The result, however the electorate votes, will mean at least 300 new MPs. Only a handful has any background in science. The scientific community will need to support these members and nurture an empathy with others to ensure the importance of science to our economy, health, the environment and social infrastructure is not lost.

They will need to be engaged in the issues rather than lectured to and above all, we need to avoid the trap of special pleading. The new Government, and back-benchers alike, need to hear a simple and consistent message about the value of science. The science budget must continue to be ring fenced and the amount within it at least maintained. If we can win the wider argument, biology has a strong heritage to call on to ensure the life sciences are not undervalued.

The Society is taking every opportunity to lobby. We have written to each parliamentary candidate to raise the profile of biology and the role of the Society but with a clear focus on the bigger picture. We are highlighting three key messages:

Recognition of the central role of science in the economy, by maintaining or increasing funding for basic and applied research in real terms. We are calling on the new Government to develop a new 10 year funding framework for science, to underpin the UK's position as a world-leading scientific nation.

The importance of practical as well as theoretical skills in the training of scientists. This will require financial support for a significant hands-on practical skills element, including lab and field skills in courses at school and university. School teachers should be enabled and supported to provide high quality laboratory and outdoor practical science teaching at all levels. We argue that particular attention is paid to this in forthcoming curriculum reviews.

The need to intensify efforts to ensure that scientific evidence is well used and communicated across government. This is necessary to improve policy development and delivery where issues cross traditional departmental responsibilities. We recommend inclusion of principles guaranteeing academic freedom of scientific advisers in the ministerial code.

There are further, more detailed arguments to make about equality of funding between the sciences, pointing out the absolute necessity of ensuring UK biology is funded in a way that enables us to retain our world-leading position. But it would be a mistake to lead the debate with special pleading for the biosciences. We need new parliamentarians to more fully understand the wide value of pubic financial support for UK science as a whole.

The recent *Question Time*-style debate organised by the Royal Society of Chemistry in partnership with the Society and others, between the science spokesmen for the three main parties – Adam Afriyie (Cons), Lord Drayson (Lab) and Evan Harris (Lib Dem) – did highlight some policy differences. And it is right to provide them with more of the detail, focussing on biology. But, they at least have a good overview of the issues. It will be the lack of science understanding across key ministerial posts and parliamentary committees that is likely to lead to misunderstanding or lack of urgency.

The Society will be working hard to build relationships with MPs and Peers post election, pushing them on their science policy and seeking to represent biology on behalf of our membership. We will develop a range of case studies on the impact of biology to support the detailed arguments and we welcome your input. But the more MPs hear the same message, the more likely it is that we will succeed. We encourage you to write to your local MP with these messages and stand ready to offer support wherever possible.

Mark Downs
Chief Executive
Society of Biology

What are the probable social impacts of the latest brain research?

Parliamentary and Scientific Committee Meeting Tuesday 19 January 2010

Having had my appetite whetted on this subject by my attendance at a Royal Society Policy Lab (reported in the last issue), I couldn't resist attending another debate on this area at the Parliamentary and Scientific Committee. An added inducement to attend was that of the three speakers, two of them are old favourites of ours, Professor David Nutt, someone that we have supported over his all-too-public sacking as a government advisor on drugs, and Professor Colin Blakemore. The third speaker, Professor David Ormorod, was a Barrister (Middle Temple) and Professor of Criminal Justice at Queen Mary, University of London. I was very pleased to see that David Nutt was given a supportive and warm welcome by the MPs and Lords present.

Nutt highlighted the sheer variety of drugs that need effective regulatory scrutiny including mental health drugs, mood-altering drugs, pleasure drugs and cognitive enhancers, not to mention new methods of delivery where, for example, you could potentially get a nicotine version of a Red Bull-type drink. This is a significant challenge for our regulatory system, which is rather haphazard, with some drugs being regulated as foods and others as medicines. There is a revolution going in brain research leading to valuable new drugs to treat conditions such as narcolepsy, age-related memory loss, and treatment of epigenetic development disorders, all of which have the potential for misuse in other contexts. But a rigid approach to regulation may not be the answer; there are problems including the regulation of hundreds of possible analogues, and the question that if we ban drugs we know something about, are we raising the risk of

people being forced to experiment with other less-familiar drugs? *Homo sapiens* has always taken drugs; perhaps the over-riding issue should be to accept this, and try to work out ways for people to do this safely e.g. by developing an antidote to counter the effects of alcohol intoxication.

Blakemore followed this up by asking whether we need something on the scale of the genome project to study the brain? The techniques for observing and potentially manipulating the brain are advancing fast. Key issues that society needs to think about are potential eavesdropping on the mind, controlling and extending brain function, and challenging the concept of choice and responsibility. Drugs have been developed to change brain function and even modulate the behaviour of children and criminals. In future will we have drugs to change attitude and satisfaction? Brain research has implications for the whole concept of personal responsibility. Some unacceptable behaviours can have a physical root in, for example, a brain tumour, and there is evidence that the conscious impression of intention follows brain states, leading to actions. So what is free will? Do conscious processes monitor decisions being made by the brain rather than driving them? Questions such as these could lead to radical changes in our legal processes.

Ormorod explored the likely use of technologies arising from brain research in a legal context. Jurors are increasingly expecting to see scientific evidence in the hope of helping them to get 'simple' answers: however, courts are very unlikely to accept such evidence in the near future. The long-established adversarial process is still vital. Technologies can never usurp the role of juries in deciding guilt or innocence. Technologies may be able to detect some lies, but this is not necessarily the same as proving that someone is telling the truth and is a credible person. Questions used in lie detector tests in a lab don't necessarily replicate those from challenging cross-examination; not all questions can be reduced to 'yes' or 'no'. In particular, issues of intention can be very murky. So there could be a danger if some defendants tried to strategically use lie detector tests to avoid cross-examination. Any technology used will need to demonstrate that it is a reliable science, backed up by a great deal of evidence, being used by an expert, and will always face problems of objections to admissibility. Lie detection might have more use post conviction, when trying to assess the risk of an individual re-offending prior to release.

The lively general discussion that followed raised the issue of designing around problems of drug use, antisocial behaviour etc. and with the possibility of technologies being used up-front to prevent crime. If society goes down this route, is there a danger that people will lose any sense of personal responsibility or moral virtue? Do we want a completely controlled community? And on that Orwellian note, we need to continue to ponder.

Liz Bell

Physiology News

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

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

The Simon Singh case, libel law reform and the free speech hustings

Our Society has been working closely with Sense About Science and its various partner organisations in their campaign to support Simon Singh in his legal battle with the British Chiropractic Association and to get reform of our unhelpful libel laws firmly on the political agenda. So we were extremely pleased to hear the news that the case against Simon had been dropped (about time too!) but this is far from the end of the battle. To try to prevent this from happening again, we need to push for proper reform of our out-dated and archaic libel laws.

With this objective firmly in mind, Sense About Science and their partners arranged an excellent pre-election hustings event on the 21st April at the Free Word Centre in London. Demand for tickets was so great that they had to video-stream it to additional venues in London, Liverpool and Nottingham. I was lucky to have registered early enough to get into the main venue and be able to see the spokesmen for the three main political parties face to face. The spokesmen on the night were Evan Harris (Liberal Democrats), Dominic Grieve (Conservatives) and Michael Wills (Labour).

The debate covered a huge amount of ground in terms of what is needed in libel reform, and highlighted it as a key defence of the free speech issue, related to free speech concerns in other areas such as under the Freedom of Information and Human Rights Acts. It was encouraging, and striking, how much cross-party agreement there is on the need for root and branch reform to the libel laws, and an apparent real commitment to work together on this. I got the opportunity to ask them, whether post election in a possible hung Parliament, the cross-party group working on libel reform could set an example to other parts of their respective parties trying to tackle other nationally important issues. I got the impression that they would do their best, but couldn't hold out any hope that a hung Parliament wouldn't break down into faction fighting on other issues.

Free speech is considered to be the cornerstone of democracy, and the UK needs to lead by example on the international scene by sorting out archaic laws that threaten to undermine this. This needs to be approached carefully. The point was made that a democracy needs to be able to protect its most vulnerable members and minorities from the 'tyranny' of the majority, and for individuals and corporations to be able to protect themselves from outright malicious defamation. But the barriers to initiating libel proceedings need to be set high enough to discourage actions against normal honest debate, and to make sure that the UK is not perceived as a haven of choice for the so-called libel tourists. Costs associated with such legal proceedings need to be seriously addressed – the personal hit that Simon Singh has taken in terms of costs and lost income was highlighted, and many individuals faced by bullying large organisations with large pots of money, are forced to retract their quite reasonable statements because of the fear of the potential financial impact on them and their families. Free speech and the public interest lose out as a result. Libel laws need to be reformed so that powerful organisations lose the ability to intimidate well-meaning individuals. The issue of providing legal aid to individuals to help redress the power balance was raised, but legal aid is already so stretched that there was not much hope that this would be possible.

One MP commented that it was disgraceful that a professional association had taken out an action against Simon in the first place. Any organisation claiming to be a learned society should be able to take and participate in robust debate. This gave me the opportunity to say that PhySoc was very much in tune with this, and that we had contributed money to the campaign to try to help sort the libel laws problems out. This was clearly much appreciated. Simon Singh made a point of button-holing me at the end of the event to stress how much our Society's support, both moral and financial, had meant to him. All three speakers told us the case for libel reform had been well and truly made, and it was the campaign that had made them see this. Sile Lane from Sense About Science told me 'It's thanks to us, and you, your Society and your readers that we've gotten to this point'. We've done some good in the world!

The Campaign is also still collecting signatures to their petition. Every signature counts as we need to keep the pressure on whatever sort of Government comes in post the General Election to keep focused on this issue, whatever other pressing economic and other issues they are facing. Sign up at: www.libelreform.org/sign

Liz Bell

International capacity building update

In the last few years, the global development agenda has moved forward to embrace the importance of science, technology and innovation in helping to address the crucial development issues facing the world today, including climate change, health, infrastructure development, the building of sustainable livelihoods and the elimination of poverty. Science and scientists are now seen to be integral to this global effort, and it is recognised that a key aim has to be to enlarge local scientific capacity in developing countries to enable them to address pressing local issues and build sustainable economies. This can only be achieved by supporting effective grassroots initiatives, tying these closely to real local needs, and embedding them in supportive governmental science policy and funding frameworks. Learned societies of every discipline are perhaps in a unique position to contribute to this agenda. So we in The Society's External Relations Policy Committee have been strengthening an interest in this with the long-term objective of leveraging extra support for physiologists in developing countries. There have been some encouraging recent concrete advances.

We have been working with the UK Collaborative on Development Sciences (UKCDS) (www.ukcds.org.uk) to create a webpage

(http://tinyurl.com/33zjjr7) on their new website publicising the contribution made by UK learned societies to capacity building. The webpage, launched in March, highlights our capacity building concept paper, the report of our meeting for UK learned societies on 2 June 2009 (Sharing our experience), and is also putting together a list of capacity building initiatives of individual UK learned societies. The UKCDS was set up in 2006 by the Secretary of State for International Development, and aims to co-ordinate the policies and activities of UK funding organizations interested in science for international development. So the creation of this webpage is a significant development, and will hopefully start to raise our visibility with policy makers. But it is important that we build up as much impressive information on the site about relevant learned society activities as possible. Our partners at the UK National Commission for UNESCO have written to a large number of UK learned societies to ask for contributions, but if you have contacts in other societies please feel free to spread the word. The more the merrier!

Our papers on this have also been picked up by the World Bank and I was invited to their Forum on Capacity Building in Washington in December 2009. I was relieved to meet a group of like-minded people there, who think that professional and society networks need to be supported in this area, including people from USAID and the African Development Bank. I will keep in touch with them as we lobby and keep you informed. Progress has already been made as a World Bank paper summarizing the event now makes reference to the role of professional and learned societies. The World Bank is an important organization to try to influence, as even though it is slow moving (so I don't anticipate any funding opportunities from there any time soon), their policy papers are well respected, and influence evolving policy agendas in other stakeholder organizations. Even the Russians are showing signs of getting interested. The Moscow-based journal *Foresight* requested a paper (based on our concept paper) which they plan to publish. Perhaps the FSB are still keeping an eye on me even though I moved back from Moscow in 2002...

The currently delightfully informal inter-learned society steering group on capacity building that we created in 2009, may also develop in an interesting way this year. Membership of the group includes the Institute of Physics, Royal Astronomical Society, the London Mathematical Society, the Nutrition Society, the Biochemical Society, the British Ecological Society and the UK National Commission for UNESCO, so we represent a strong cross-disciplinary coalition. The group plans to hold some further workshops this year, and may become formally constituted as a committee under the UK National Commission for UNESCO. If that happens we may have to stop being enthusiastic and raucous in our meetings and look more staid and serious! We're also brainstorming how the Biochemical Society's mentoring scheme in Nigeria might be developed into a bigger programme involving other societies.

So watch this space. You're very welcome to get in touch with me (ebell@physoc.org) if you have any thoughts on how to develop this agenda further. Interestingly, we are starting to get on the media radar. SciDevNet, a key resource for news relating to science and international development, has published two articles on learned societies and capacity building that I have been involved with. These can be viewed at: http://tinyurl.com/yceywzr and http://tinyurl.com/2wfju5p

Liz Bell

HIT press splash

An article in the 15th March edition of *The Journal of Physiology* created a media splash when the press release hit newswires last month. About short-term high-intensity interval training (also known as HIT), the new research from scientists at Canada's McMaster University shows that HIT is a time-efficient but safe alternative to endurance training. The tag line: do less exercise, get better results. The story was picked up by the *Metro*, *Daily Telegraph*, *Independent*, *Los Angeles Times* and *CNN*, to name just a few.

Call for media volunteers

The Physiological Society is now making a greater effort to interact with the media and increase the profile of physiology. As part of this initiative, we're updating and expanding our database of Members who have media experience and are leaders in their area of research. If you can help by registering as a media contact, please email Mary Arbuthnot (marbuthnot@physoc.org) with the following information:

1. Your name, location and contact details
2. Your area(s) of speciality, especially on topics often of interest to the media
3. A summary of any previous media experience (i.e. print, radio, television)

Media training for young physiologists

Are you an Affiliate Member looking to gain more experience communicating your research to the media? The Physiological Society works in partnership with Sense About Science to sponsor young physiologists to attend their ongoing 'Standing up for science' media workshops. Affiliates who attend this course have the opportunity to become spokespeople for physiology as well our Society. For more information, please contact Sense About Science (see also p. 31).

Members in the news: please stay in touch!

Have you recently been the subject of a press release put out by your university – or will you be in the future? The Physiological Society would like to know. We have a new page on our website specifically devoted to Members in the news. Please contact Mary Arbuthnot (marbuthnot@physoc.org) with the details.

Reflections from a retiring President

In the beginning...when I became President of The Society in 2008, I summarised what I perceived to be the important issues facing The Society, in a paper for its Executive Committee:

The Society has a long and distinguished history, during which it has played an active role supporting and promoting Physiology. During that time Physiology has changed, and continues to change ever more rapidly, particularly as traditional borders become blurred, so that Physiology now spans from molecule to translation – areas traditionally associated with other disciplines, such as Biochemistry and clinical research.

The Society has risen to the challenge, not only of a changing discipline, but also the changing expectations of Members and the changing environment in which it operates: increasing internationalism, increasing demands on time, and increasing numbers of meetings, all place pressure on The Society. The recent re-organisation of The Society's committee structure to reflect its major aims, underpinned by professional and well run offices, and re-branded to give coherence to its identity, will all help The Society achieve its aspirations. The challenge now is to build on this foundation to ensure that The Society continues to develop, and continues to be relevant and important – and to be regarded as such – in supporting and promoting Physiology, nationally and internationally.

This will involve very specific challenges, developing activity in each of the areas represented by our major committees, as well as developing international activity, deciding how we best interact with our sister societies, and how we support the translational aspects of Physiology, while continuing to support our core science and activities. It also involves more generic considerations:

Modernization. The Society is sometimes seen as somewhat old fashioned. While I don't believe that this is the case, we need to continue to work to demonstrate that we are forward looking and developing with our science, while keeping the excellence traditionally associated with The Society, so that The Society is seen as the leading light in the discipline.

Increasing ambition. In all areas of current activity – Education, External Affairs, Meetings and Publications, as well as international activity and new areas, such as translation, we should continually be looking for ways to increase the scope and range of our activities, while maintaining our focus. This is important, not just to support and promote Physiology now, but also – by providing relevant activities and information – to ensure that we publicise Physiology, attract people to the discipline, educate people about its importance, and thus help ensure its future.

Increasing sphere of influence. To meet the challenges outlined above, it is important that we not only increase our activities, but that we engage with a broader range of people: teachers, pharma and clinical colleagues, as well as continuing to broaden our appeal to undergraduates, postgraduates and post-docs, to develop links with other societies, and to increase our international activity and political influence. Some of these activities will be best pursued through the Society of Biology, others by The Society itself, for example by increasing and broadening its membership. Physiology is central to the life sciences; it is our responsibility to ensure that it is seen as such, and to ensure that The Society is central to Physiology.

Transparency. The Society needs to ensure that communication with colleagues is clear and transparent. This becomes harder as traditional Physiology departments disappear, but also becomes more important if the disappearance of departments is not to result in the disappearance of the discipline. Without such communication it is going to be difficult to engage properly with Physiologists, and thus to ensure the future of Physiology as a discipline. There are obviously many routes to achieve this – email, web surveys and the web site; PhySoc reps, SIG convenors and HoDs groups; the magazine and newsletter; attendance and advertising at meetings – we need to ensure that we use them as effectively as possible.

If The Society is to continue to support and promote Physiology effectively, and to be seen as central – relevant and important – to the discipline, we need to ensure that we provide appropriate resources to the widest relevant constituency, while maintaining our focus. Where this focus should lie, and the future of Physiology and of The Society itself, are broader and more challenging questions; however, they will also be important when considering the future.

Two years later... my period of office as President of The Physiological Society is finishing at the AGM in Manchester in June. It has been an honour and a pleasure, and I know that when I finish I will miss it greatly. I also know, however, that Mike Spyer, who takes over from me, will bring fresh energy, enthusiasm and ideas, which will enable The Society to continue to flourish and grow.

When I started, I had a hard act to follow: Ian McGrath as Chair, with Ole Petersen as President, had restructured The Society so that its main committees (Meetings, Publications, Education, External Affairs) reflected more closely the main goals of The Society, and enabled the committees to work more effectively with The Society's offices. Ian and Ole had also overseen a rebranding of The Society and started to ensure that The Society and its journals worked more closely together.

I had worked with Ian, as vice-Chair, while these changes were introduced. I was pleased, therefore, that when I

started my term of office, I had firm foundations to build on. The question was, what to build? Although – as I am sure many of my colleagues would tell you – I don't shy away from change, I am not a believer in change for its own sake; it has to serve the needs of the organisation. The Society has undergone a lot of change (in my view for the better) in recent years, bringing a modern and professional approach to its activities. My first aim, therefore, was simple: to allow these changes to establish themselves and 'bed in'. However, given that The Society was now organisationally and financially stable, my second aim was to take advantage of this position to develop long-term plans, and to increase the range and scope of The Society's activities while remaining focussed on its key areas of activity. I knew that this was going to be the start of a long game which, although it would not have immediate impact, would be important for the future of The Society. As a result, The Society now has a 5 year strategic and business plan for its activities, including development of its interest in translational science, while retaining and building on its traditional strengths. This will remain an active document, under continual review and development, to guide The Society's activity and development. There are planned developments in all of The Society's activities – from Education and Outreach, to Publications and Meetings – and there are increasing collaborations with other societies around the world and increasing focus on translational science.

None of this would be possible without The Society staff in London and Cambridge, under the guidance of our CEO, Mike Collis. You meet some of them at meetings, talk to some of them when you submit papers to the journals. You might not, however, be aware of quite how much they do for The Society: they are frequently our 'public face' for enquiries, they look after our finances, design and produce our publicity material, organise and run meetings, administer memberships and grants, run our IT, look after our international activities and publications, develop educational resources, organise and participate in workshops and outreach activities, and co-ordinate our response to government and other consultations. If you read *Physiology News* and look at the website you will see just how much The Society does. I have been proud to be part of it, and would like to thank all of those who make The Society work: we have an outstanding team of committed, creative, enthusiastic and professional staff, under the very able leadership of Mike Collis, with whom it has been a pleasure to work.

Looking back, there have been too many highlights to list in full: Society meetings, including Prem Kumar's after-dinner speeches as Meetings Secretary, the quality and diversity of the invited lectures, watching young scientists give their first presentations, meeting friends and colleagues, and welcoming guests from around the world; seeing the activities of The Society develop and grow; working with other societies both nationally and internationally, particularly at the IUPS meeting in Kyoto and the joint meeting in Beijing, both of which provide viable models for future ways of societies working together. This is, I think, central to the future success of our discipline: networks of physiological societies working together across the world, using new technologies to reach new constituencies, and ensuring that physiology is seen for what it is: the discipline that is able to link and integrate the biosciences.

So what next? For me, more time for the day job, as Dean of the Faculty of Medical and Veterinary Sciences at the University of Bristol. For The Society, to continue to develop and run its activities and to plan for future activities, including a meeting in London to celebrate the Olympics in 2012, and the International Union of Physiological Sciences meeting in Birmingham in 2013.

As President I have had the honour of representing The Society, and the pleasure of working with great people – in the offices, at Exec, in Council – to help ensure the well-being and development of The Society that supports our discipline. I thank all of them for making my term of office so enjoyable and rewarding, and would encourage anybody who might be interested in being involved – from putting forward ideas and suggestions, to serving on its committees – to get in touch with The Society; it enables you to broaden your horizons and see your discipline in a new light, as well as providing the opportunity to help shape the future of The Society and the discipline.

Clive Orchard

New staff member

Mary Arbuthnot

I was excited to join The Physiological Society in February as the Media & Marketing Manager – a brand new position! I grew up in the San Francisco Bay Area, where my parents still live, but thanks to an English mother I'm a dual US–UK citizen with lots of family in England. In 2005 I decided to return to my roots and relocate to London after four years living in New York. It was the best decision I've ever made!

I have a background in science documentaries and have worked for a wide range of production companies, including a stint at the BBC. My television claim to fame was working on the popular natural history programme *Meerkat Manor*. More recently I've been exploring a career change to science communications, and before joining Physoc I worked at both the Science Media Centre and the Science Council.

Last May I got married to my husband Stephen. We live near Wimbledon and are a holiday destination for many of our friend's cats. We're very into our local farmer's market, nice wine, tennis and politics/current affairs.

Farewell to Mike Collis

It was with regret that in April we received Mike Collis' letter of resignation as CEO of The Society. Mike's last day with The Society is likely to be 9th July 2010, just after Physiology 2010 in Manchester. Mike joined The Society in May 2006, after a successful career in Pharma (see '*Thoughts on the evolution of a scientific career*' which Mike wrote for *Physiology News* **64**, Autumn 2006: http://tinyurl.com/pnews64), bringing with him a wealth of scientific and managerial experience. He joined at a time when The Society's offices and governance structures were emerging from a period of change, engineered by Giovanni Mann as Chairman and Alan North as President, when a steady and resolute hand on the tiller was required.

In his four years as CEO, The Society has benefitted enormously from Mike's experience, expertise, advice and hard work. During his first two years with The Society, working with Ian McGrath as Chair of the Executive Committee, and Ole Petersen as President of The Society, Mike oversaw the development of The Society's offices, and re-organisation of its committee structure, to reflect better The Society's main objectives and to enable the offices to provide the best possible support for The Society's activities. At about the same time The Society underwent a re-branding exercise to bring coherence to its different activities, and subsequently underwent a change of governance, in which the roles of Chair and President were merged into that of President. Mike's steady hand helped ensure that these changes were realised with the minimum possible disruption.

In the last two years, Mike has helped The Society build on the foundation provided by these changes to develop and expand its activities, and to bring increasing professionalism to the way in which The Society runs. The benefits of this are clear, both in what The Society provides and the way in which it is provided: The Society is running more smoothly and effectively than ever, while delivering a wider range of resources and services (see Mike's review in The Society's annual report for 2009). Part of this success can be attributed to Mike's success in developing The Society's offices: Mike has always supported and developed The Society's staff and as a result we are fortunate to have dedicated and creative people working as a team to support and help deliver The Society's activities.

Throughout all of this, as well as being thoughtful and effective, Mike has been a pleasure to work with. It is typical of his approach that Mike is stepping down at a time that he thinks is right, not just for himself, but also for The Society, to enable it to realise its own plans for the future, while at the same time wishing to do all he can to minimise the disruption of appointing a new CEO to work with the new President – Mike Spyer – who starts in July 2010. As well as thanking Mike for helping to put The Society where it is today, we are sure we speak for all Members when we wish him all the best for the future, which will continue to encompass activities with the scientific community as well as, among other things, French vineyards.

Ian McGrath, Clive Orchard and Mike Spyer

+++ Win a netbook +++

Tell us your views on *Physiology News* and win a netbook

We want to hear what you think of *Physiology News* – too much of something, not enough of another? Fill in our short survey and one lucky respondent will receive an electronic netbook – to be entered for the draw please make sure you include your email address or membership number.

http://www.surveymonkey.com/s/magsurvey

Science in the public eye – engagement opportunities for research scientists

Our affiliate representative, Sam Passey.

For many people, a career in scientific research means just that – sitting in the lab everyday performing experiments in their chosen field and writing the odd paper or poster to present their work to other scientists in the same or related fields. However, a research career can include much more than that, and as many of us in research in the UK are funded through public money from research councils, we have a duty as scientists to communicate our science to a wider audience and actively include the public in our discoveries and difficulties.

Public engagement in science is a broad term that encompasses a huge range of activities from public debates about important scientific issues, through to science fairs and schools events that demonstrate and highlight the science of the amazing world in which we live. Communication of science, and in particular the biomedical sciences such as physiology, with the general public is essential and has many benefits to both scientific research and also the public appreciation of the work that scientists do and how this benefits them. In recent years, many researchers have gained high profiles through their science communication efforts including renowned anthropologist/anatomist Alice Roberts who has appeared in a number of TV series such as '*The incredible human journey*' and '*Dr Alice Roberts: don't die young*', Professor Jim Al-Khalili who has presented TV series on '*Science and Islam*', '*Atom*' and the upcoming '*Genius in Britain*' in 2010, and Professor Brian Cox who has recently shot to fame with his recent series '*The wonders of the solar system*'.

However, engaging the public in science does not require fame and a

TV series but includes the numerous public science events, large and small, held up and down the country every year that provide opportunities for research scientists to participate and help communicate their research to the wider community.

So what are the advantages of participating in public science engagement? There are many direct benefits, including development of essential skills in communication and learning to convey scientific ideas to a range of audiences in a context and a language that everyone can understand. Listening is an important skill too, as real engagement with the public about scientific issues must be a two-way dialogue in which researchers listen to the opinions, ideas and concerns of the public.

Having participated in a few science events for both schools groups and the wider public at larger events like the '*Science Alive*!' event in Bristol, I have very much enjoyed the opportunity to listen to people's thoughts on scientific research and to discuss science and my research with those who may see things differently from myself. People not working in research often have completely different viewpoints and ideas about how your research is important, and the process of discussing your work in a new environment and different context can help you to see things in an alternative way that can inspire new directions and help progress your research. Also, at times when you are feeling particularly low about your research project, presenting the work to people who find it new and exciting can inject new life into the project and make you see it in a fresh light. For me, seeing the enthusiasm and curiosity that both children and adult visitors have and the looks on their faces as they observed and learnt about different physiological or biochemical processes was hugely rewarding.

Presenting and communicating your work to people outside your research field can also lead to new contacts and even future collaborations in other fields, and enhance your career prospects as your contributions are recognised. The recently published booklet by Research Councils UK entitled '*What's in it for me? The benefits of public engagement for researchers*' contains numerous accounts of how contributing to science communication has helped to enhance careers and even lead to early promotion.

Some of the public science events held in the UK

- Cheltenham Science Festival
- Edinburgh Science Festival
- British Science Festival
- Cambridge Science Festival
- The Big Bang
- Science Alive!
- National Science and Engineering week

Perhaps one of the most important aspects of participating in public science events is that it is fun! Although often hard work, many people find these events very enjoyable and the idea of inspiring people to appreciate the world around them and perhaps even think about a career as a scientist is very motivating, at least for me.

So what opportunities are there to participate in public science events? There are numerous avenues to explore in this area, and many public science events are held all over the country on a regular basis.

These festivals cover a wide range of topics, but typically include medical/physiology-related events such as the '*Engineering human tissue*' and '*Heart attack*' events that are scheduled for the Cheltenham Science Festival in June this year. There are also a number of smaller workshops and school-targeted activities. Many universities participate by putting together demonstrations and workshops; indeed The Physiological Society has also participated in a number of these events including the *Big Bang* which was held in Manchester earlier this year.

Many research councils and funding bodies offer funding for public engagement in science events, including the Wellcome Trust, whose Engaging Science grants programme actively supports projects that are aimed at communicating with the public about current biomedical research and its implications. The Physiological Society runs an Outreach Grant scheme, which can provide funds to support outreach activities that promote physiology to the public and to schools groups. These events can be run as part of a larger festival such as those mentioned above, or as a stand-alone event for the local community or local schools. For example, recent events funded by the Outreach scheme include '*Physiology in action: The science behind exercise – promoting science and biomedicine to the public*' which was organised by Kevin McDermott and colleagues and held at the University of East Anglia (see p.46) to promote the physiology of exercise. Another one was the interactive neuroscience workshops held at Cardiff University School of Biosciences and organised by Sheila Dargan and colleagues as part of National Science and Engineering week (see p. 46). These events are often very popular and receive good feedback from visitors and organisers alike. For more information about the PhySoc Outreach Grants scheme, take a look at the Grants section of the PhySoc website at www.physoc.org.

For those who have participated in public science events and perhaps wish to explore further into the world of science communication, there are also a number of opportunities to gain more formal training in this area. For example, the British Science Association offers Media fellowships that involve a work placement of 3–8 weeks with a journalist working for the national press, broadcast or internet-publishing fields, allowing science researchers to learn about communicating science in the media and enabling them to develop essential skills that help them to communicate their own work better when they return to the lab. Other opportunities include the Royal Society Media Training and Communication Skills courses, and the Wellcome Trust Biomedical Science Media studentships that offer formal training and a post-graduate qualification in Science Media Production at Imperial College London.

Even for those of us who are not envisaging a career in the media (we are scientists after all), participating in such events offers many potential benefits – if only just to escape from the lab for day, to have a bit of fun, to see people being amazed by science and to remind ourselves that being a research scientist can actually be pretty exciting at times.

Sam Passey

Ask a physiologist!

Why have humans lost body hair as opposed to keeping it as a method of keeping warm? (Mark, age 17)

Dr Fred Imms, formerly of King's College London, replies:

Most mammals including primates have body hair and one of its functions is a defence against cold. Humans do have some body hair notably on the scalp, perhaps to protect from radiant energy, and adults have pubic and axillary hair. Whilst abundant body hair protects against cold, it reduces the ability to lose heat in hot weather.

Hairy skin has many apocrine sweat glands, which together with sebaceous glands, produce an oily secretion. Evaporation of this sweat is impeded by hair, which becomes wet and matted and although some heat loss occurs via this route, it is inefficient. Furry animals have developed other methods of coping with hot conditions. For instance, dogs increase their evaporative heat loss by panting and other species have become nocturnal to avoid heat. Humans have apocrine sweat glands only in the axillary and pubic areas.

Most areas of human skin have large numbers of eccrine sweat glands, which produce a watery secretion when body temperature rises. This evaporates to increase heat loss from the body. During exercise in hot conditions over one litre of sweat may be produced each hour and up to 2000 kJ of heat can be lost. Our hairless state has thus enabled us to cope more effectively with heat challenges. To cope with cold stresses, we wear clothing as an artificial fur to provide insulation and reduce heat loss. Man has thus gained an evolutionary advantage over furry animals by increasing our physiological ability to cope with hot conditions whilst developing strategies to protect against cold.

Why are our fingers different lengths? (Alistair, age 18)

Dr Glenn Baggott, Birkbeck, University of London, replies:

As there are a lot of fingers I will concentrate on the length of the index finger (the one next to the thumb) relative to the ring finger, as men have an index finger shorter than the ring finger. However, the relative lengths of these two fingers vary within each sex, and remarkably these differences are associated with some characteristics of human sexual behaviour. Men with longer index fingers exhibit more jealousy towards rivals, whereas men with shorter index fingers are more aggressive towards male competitors and have much younger women as partners. They also have higher sperm numbers, are married to women with the longest index fingers and produce more children. How can this be?

The variability in finger length seems to be due to exposure of the fetus to differing levels of the male hormone testosterone. For example, some fetuses have tissues insensitive to testosterone and so grow relatively longer index fingers whereas others produce excessive amounts of the hormone and so have smaller index fingers. Girls from non-identical boy/girl twin pairs have shorter index fingers than non-identical twins where both are girls. Higher testosterone in the womb produces more masculine characteristics in the adult.

Even more intriguingly, other aspects of human behaviour, such as competitiveness, are associated with the relative length of these two fingers. Professional footballers have relatively shorter index fingers compared to non-professionals, first-team players have shorter index fingers than reserve players, and international players have the shortest index fingers. As the length of this finger is associated with certain aspects of human reproduction, it's clear that professional footballers can do much more than bend it like Beckham.

Where and how is memory stored? (Kay, age 17)

Dr David Wyllie, University of Edinburgh replies:

This is one of the 'big' questions for which we do not yet have a complete answer. The human brain contains upwards of 100 billion neurones (nerve cells) which form a network that continuously sends and receives signals, then processes them to control every aspect of our behaviour – from simple tasks such as breathing, to the complex such as perceiving emotion, or recalling memories. Neurones 'communicate' with each other at specialised sites called synapses where one neurone releases a chemical (a neurotransmitter) that binds to specific proteins (receptors) on a second neurone. A major neurotransmitter in the brain is glutamate and its receptors play a critical role in memory storage. When glutamate acts on its receptors, positive ions such as Na^+, K^+ and Ca^{2+} flow though a pore in the receptor producing a tiny electrical signal in the neurone and this is the starting point for communication between brain cells.

Glutamate synapses can undergo a process called 'synaptic plasticity'. What does this mean? Put simply, if two neurones communicate with each other a lot, then a remarkable thing happens – efficiency of the communication between them increases. This idea was first suggested by D. Hebb in the 1940s, but demonstrating this effect took many more years. Experiments performed by two physiologists, T. Bliss and T. Lømo, and published in *The Journal of Physiology* in 1973 reported the discovery of the phenomenon we now call 'long-term potentiation'. This is the process now considered to be a mechanism by which memories are stored.

So where is memory stored? One answer to this is part of your question is 'at synapses'. However, you are probably asking where in the brain are memories stored. Well, it depends on the type of memory. We have 'working memory', which you are using right now so you can make sense of what you are reading. We also use working memory to do mental arithmetic, or to remember a telephone number. Working memory is thought to be stored in the frontal and parietal lobes of the brain. We also have 'long-term memory', which can be divided into several types. 'Semantic memory' is our ability to recall facts e.g. giraffes come from Africa, and the basal ganglia and cerebellum are important for this. Next we have the ability of recognising situations that alter our emotions – we feel comfortable when surrounded by our family and friends but may become fearful in an unfamiliar situation. The amygdala plays a vital role in emotional memory. Finally, we need to consider what we refer to as 'episodic memory', which we use to recall our own experiences. The hippocampus is important for this type of memory. Use your episodic memory now to recall what you had for dinner last night. Most of you will be able to do that quite easily. Now what did you have for dinner three weeks' past on Tuesday? Unless that date was a special event, such as your birthday, you are unlikely to recall what you ate. This is a feature of episodic memory – we find it easier to recall events if they are associated with other significant events. So for those of us who have no special association with that date, remembering that meal will need us to recall some other event that happened!

Recent educational outreach activities at The Physiological Society

The Society is keen to support outreach activities that engage school students and the wider community with physiology. This article provides a summary of the activities we have supported so far this year, and we are planning more for the future. If you are interested in running an event, we would encourage you to apply for an Outreach Grant.

The Big Bang Fair, 11–13 March

With three times as many visitors attending this year, compared with 2009, the Big Bang Fair in Manchester was undoubtedly a success and The Physiological Society was proud to play a part. The remit of the Big Bang Fair is to promote STEM careers to young people and address related skills gaps across the UK.

With this in mind, The Society sponsored two activities at the Fair: the mobile teaching unit (MTU) and the winter biathlon challenge.

The MTU is a lorry that expands into a seminar room to facilitate group teaching sessions; however, at the Big Bang Fair, it was used as a drop-in facility with activity stations situated around the lorry. This resource offered visitors an opportunity to use a range of clinical equipment to learn more about how the heart, lungs and nervous system work. Each activity was designed to enrich current topics based on human physiology in the national curriculum. The Society was pleased that several of our Affiliate Members were available to assist teaching staff from the University of Bristol, who regularly take the MTU to visit schools.

The second activity was the winter biathlon challenge, organised by Valerie Gladwell and assisted by staff from the University of Essex, University of Manchester and ADInstruments. Jason Sklenar, the GB Biathlon Coach, was also on hand to provide a personal perspective. Hundreds of participants took part in the activity, which simulated the physical and mental challenges of the Winter Biathlon. We would like to thank ADInstruments for their generous sponsorship of this event.

Both activities received a good response and we hope The Society will be represented at the Fair again next year.

Big Bang 2010: winter biathlon challenge.

Outreach Grants

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

National Science and Engineering Week (NSEW), 12–21 March

Three Members of The Society received funding through the Outreach Grant scheme to run events during NSEW.

Sheila Dargan of Cardiff University hosted neuroscience-themed workshops for 240 primary school students aged 9–11 (see Report 1, opposite).

Continuing the neuroscience theme, Stephen Fitzjohn of the University of Bristol presented an exhibition stand entitled ‘Mouldable minds: making memories stick’ at ‘Discover 2010’, which was a free interactive public exhibition held by Bristol in local shopping centres (see Report 2, opposite).

Kevin McDermott of the University of East Anglia hosted a stand centred on the theme of ‘Physiology in action: the science behind exercise – promoting physiology and biomedicine to the public’ at the Forum in Norwich, an event that was free and open to the public (see Report 3, on p. 48).

Outreach workshop

If you would like to find out more about how you can get involved in running an outreach event for schools, please come to our Outreach Workshop at Physiology 2010.

Further details are at: www.physiology2010.org

Report 1

Following the recent appointment of Ole Petersen as the Director of the School of Biosciences at Cardiff University, we were keen to increase the amount and range of physiology-based workshops on offer to pupils during National Science and Engineering Week.

An Outreach Grant from The Physiological Society enabled us to purchase materials to run new interactive workshops to inspire pupils and improve their understanding of key aspects of physiology. The workshops were developed by the School of Biosciences in collaboration with Cardiff Neurosciences Centre, and were led by more than 30 enthusiastic volunteers including undergraduates, PhD students, post-docs, research fellows and lecturers. The workshops were part of a well-established award-winning event '*Learn about Life*', which this year attracted over 240 pupils (aged 9–11 years) from six local primary schools. To maximise the impact of our new workshops we also ran some of these activities at the local science centre, *Techniquest*, which attracted several school groups (age ranges 7–14) on the Friday and general public on the Saturday, enabling us to engage with adults as well.

Students create 'neurons' using pipe cleaners and Skoobies, and stick them on a poster of a 'giant brain'.

Some examples of the interactive workshops:

Brains: caps, cells and surgery. Workshop leaders explained how different parts of the brain have different functions whilst pupils drew brain lobes on caps. Pupils also made brain cells out of craft materials whilst learning how synapses allow neurons to communicate with each other. Students also had a go at brain surgery: dissecting grapes (representing tumours) out of jellies (brains) to illustrate how delicate brain tissue is.

Sensation station. Students learnt about the sensory and motor function of nerves using interactive hands-on activities including the 2-point discrimination test, drawing around a pupil and 'filling in' the physiology and constructing neuronal networks.

Sheila Dargan

Report 2

On 11–13th March, the University of Bristol ran the *'Discover 2010'* exhibition in the Mall Bristol shopping centre. This biennial event showcases the university's latest research to the general public and is organised by the Centre for Public Engagement (CPE), with groups of researchers volunteering to put on stalls. The neuroscience group was led by Charlie George and also included myself, John Gillespie, Maddy Foard and Victoria Wallace. Having come up with a vague plan and some activities based on 'memory', feedback from the CPE and Anne Cooke suggested we focus even more on the theme of '*Making memories stick*'. We devised a series of activities including 'smell pots', in which people were asked to identify the smell as well as whether it triggered any memories; animations showing how neurons and synapses work; an MRI scan of a brain, along with model brains, information sheets and the Bristol favourite of making neurons out of pipe cleaners. Our memory test was replaced with some snazzy computer and drawing-based tasks organised by colleagues from Experimental Psychology who, led by Chris Kent, were a great addition to our stall.

'Discover' exhibition stand in Mall Bristol shopping centre.

We were helped by a group of 15 volunteers who approached the event with immense enthusiasm. Having students rushing over to your stand is a bit daunting at first. 'What do I say to them?' being a common question but once you're engaged with them, it's great fun. Mixed in with the schools were the general public, which was daunting in a different way. You never know what people are going to ask but they are really just keen to talk to you, and they don't expect you to have all the answers. Leaflets from the DANA foundation and The Physiological Society were gratefully taken by many people. The financial support we received from The Society helped us buy a new brain model and replenish our stock of leaflets. The event was also a great opportunity to see what other research is going on in the university. In the end, we finished feeling tired but very enthusiastic about public engagement. Roll on the next event in two years.

Stephen Fitzjohn

Report 3

Sunday 21st March was an eventful day in Norwich. As well as the various events going on to celebrate National Science and Engineering Week, it was also the day of the Sainsbury's Sport Relief Mile, which saw thousands of people of all ages, sizes and fitness levels descend on Norwich city centre to run races to raise funds and awareness for good causes. With exercise and fitness at the forefront of everyone's mind, I was keen to use this as an opportunity to promote physiology, and the science behind exercise and physical fitness.

With my collaborators, Dr Mark Williams and Richard Kelwick, we developed an event entitled '*Physiology in action: The science behind exercise – promoting science and biomedicine to the public*'. Activities included demonstrating EMG activity, reaction times and lung function; we took the opportunity to provide advice on preventing heatstroke, injuries, optimising hydration and nutrition strategies. We also engaged with A-Level students considering studying science at school, university and beyond. By the end of the event, we were confident that there were several young people now enthusiastic about a career in physiology!

I would encourage physiologists in all areas of research to engage in outreach activities and to help dispel myths that surround science and scientists. I would like to thank Chrissy Stokes who has been a great source of help in organising this event and The Society for awarding me an Outreach Grant.

Kevin McDermott

ASE Annual Conference 2010

Despite the poor weather conditions, the Annual Conference of the Association for Science Association went ahead as planned at the University of Nottingham on 7–9 January. The Physiological Society once again shared an exhibition stand with the British Pharmacological Society and the Biochemical Society, providing us with an opportunity to speak directly with science teachers and promote our new Contacts scheme (please visit our website at www.physoc.org/schools for more details), which received a lot of interest. We also launched our first competition for schools: '*Why do we use animals in research?*' Congratulations to the winners Izzy Raywood (16) of The King's School Ely and William Rhodes (16) of Bedford School, whose entries are on the right. Both winners received a £50 Amazon gift certificate and £100 for their school.

We also collaborated with the Society for Endocrinology to sponsor a talk by Tony Michael of St George's, University of London, entitled '*Making new genes: the role of hormones in reproduction*'. This talk was part of a series that we run together with several other bioscience organisations each year, entitled '*Biology in the real world*'. Each presentation and the accompanying programme can be downloaded at our website at www.physoc.org/education.

The Society will exhibit at next year's conference, hosted by the University of Reading on 5–8 January: the title will be '*Biologists today and tomorrow*'.

School competition winners

School students had to answer the following question in their own words: '*Why do we use animals in research?*' Here are the winning entries:

Izzy Raywood (16), The King's School Ely

The development of drugs and medical technologies that help to reduce suffering among humans and animals depends on the carefully regulated use of animals for research. Many people disagree with animal testing because they believe humans should not cause an animal pain, suffering, distress or lasting harm. However, using animals such as dogs, cats, rodents and monkeys we have found cures for many diseases and illnesses including the cure for polio. Diabetics would suffer or die from their disease without the help of animals. Also we would not have the benefit of advanced antibiotics and other anaesthetics and vaccines that we now take for granted.

However, testing on animals could also benefit animals. Scientists are currently trying to find cures for many animal diseases using animal testing. Animals are biologically similar to humans. They are likely to get many of the same health problems, in addition they live short lives and most of them reproduce well so research can be carried out easily on the same species. Scientists can also easily control the environment around the animal e.g. their diet, temperature, surroundings etc. to help carry out research. The basic reason for animal trials is to determine two issues before any new compound is introduced into a human: safety and efficacy, whether a compound is safe for human ingestion and also whether or not a product works for its intended purpose.

William Rhodes (16), Bedford School

Animals are used in research to predict the reactions of humans to a medicine. Animals are a necessity in the current world for research; without animals, the medicines and surgical procedures that we use today and take for granted wouldn't exist. Antibiotics, vaccines and anaesthetics were all created through the use of animal testing. Animals serve as a 'test run' for newly discovered medicines, to make sure they are safe to use and able to improve the life of a human. But perhaps in the modern world, with technology currently booming, animal use in research may be replaced by computer simulations that accurately predict an animal's response, yet it is unlikely these could ever model the complex interactions of an entire living organism.

The fact is we only use animals in research because there is no other option. The human race faces a choice: we could decide not to use animals in research, and agree to lose the lives of many people in the world to diseases that could be treated. I believe that we will continue to do everything it takes to reduce the suffering of humans, whilst reducing the use of animals in research where possible.

The Society would like to thank John Meredith (Understanding Animal Research) and Paul Andrews (St George's, University of London) for their contributions to judging this competition.

In search of physiology – ask Google

If you are investigating a particular aspect of physiology – perhaps for a study assignment, to teach a class, or as part of a research project – how do you look for relevant information? The library? E-alerts to your favourite journals? PubMed searches? What about Google searches? Do you sometimes – or often – turn to Google for answers?

Your preferred method probably depends on whether you are part of an academic institution with all its resources for accessing scholarly literature. Or does it? A recent survey of how researchers at US universities access information (http://tinyurl.com/yc36rpd) reveals that use of general search engines is growing faster than use of more subject-specific electronic research resources. In the publishing world, we thought that only undergraduates accessed scholarly publications via Google, but this survey shows that career researchers also use this method to find content.

It is perhaps not surprising that younger academics who have grown up with Google are comfortable using it as a tool in their work life. If they have learned how to create effective searches then why not continue to use a product that covers the whole range of online content? But this presents a challenge for producers of scholarly content on the web. If the people we want to find our content – your research paper in our journal – are using Google to look for it, how do we compete with the numerous sites providing information on common health issues that dominate page 1 when we type 'blood pressure and exercise' into Google?

Non-technical summaries – who's finding them?

Getting our content to the notice of Google searchers is especially topical for *The Journal of Physiology* at the moment because we have introduced non-technical summaries for all research papers. Our aim is to help non-specialists, who come to *The Journal* site, understand what the papers are about. Our target audience is non-specialist researchers or professionals who find the journal site through keyword searches (internet 'browsing'), undergraduates or even high school students researching topics for assignments, patients or carers researching specific pathologies, or science journalists looking for copy. All of these groups may use a range of means to find *The Journal*'s site, but the most likely route will be via Google.

The Journal of Physiology

We have always constructed our online content to ensure that it is ranked competitively in Google search results, but these survey results and our new outreach initiative make this objective even more important. We are implementing a number of new measures to ensure the journal websites in general and *The Journal of Physiology* non-technical summaries in particular are listed early in search results.

Helping Google find our content

Search engines, such as Google, use small scripts called 'robots' or 'spiders' to regularly crawl over websites and index their content – it's this process that allows a site to be visible as a search result. We can improve this search visibility by adding keywords and descriptions to all our page templates. This labelling, or 'meta tagging' using physiological-related terms, will allow Google to index and display our websites when such terms are searched for. We are also adding descriptive text to our homepages – again to increase indexing.

Google also prioritises its indexed content. For example, text titles and subtitles often rank higher in search results than body text. For this reason, we will be labelling non-technical summary text using these title, or header style, tags. This will allow the content of non-technical summaries to be more prominent in Google search results.

Spreading the word about physiology

In addition to these background improvements, we are also working with authors to ensure that the non-technical summaries for their *Journal of Physiology* papers match the audience most likely to find the paper. Papers on highly technical molecular mechanisms are more relevant to researchers in allied fields than to patients or science journalists. This audience can cope with a reasonably high level of technical terminology but will still need the help of a simplified summary to judge whether the material is relevant to their research focus. They should have little trouble finding the summaries through Google searches, if this is their preferred method, because they are likely to use sophisticated search terms which limit the number of results found.

On the other hand, papers on obesity or ageing are of direct interest to a much wider range of readers and we need to work more carefully with authors to ensure that the summaries are pitched at the right level and describe the importance of the paper in terms that will be understood and used by the non-specialist. Our aim here is to take physiology to a wider audience and build an appreciation of the significance of the work that is published in *The Journal of Physiology*. Our 'partnership' with Google is key to this endeavour.

Carol Huxley
Liam McKay

Faculty of 1000

Faculty of 1000 is a unique online service that helps you stay informed of high impact articles and access the opinions of global leaders in biology and medicine.

The Physiological Society has teamed up with F1000 to make available each month up to three evaluations from F1000 of articles that were published in *The Journal of Physiology* and three evaluations of articles from *Experimental Physiology*. These evaluations help to put the articles in context and provide opinion and perspective from leading scientists working in the field.

Ronald James Linden

3rd April 1920–11th April 2010

MB ChB, PhD, DSc, FRCP
Emeritus Professor of Cardiovascular Physiology, University of Leeds

Ron Linden was 90 years and 8 days old when he died suddenly and unexpectedly from a heart attack on 11th April. Only a week before, he had enjoyed his 90th birthday party with his three sons and their wives, eight grandchildren and five great grandchildren present.

Ron was the epitome of rugged individualism and Yorkshire bluntness. He was born in Scriven, Knaresborough, the second son of a Master Grocer, Alfred Linden. He won a scholarship to Knaresborough Grammar School (of which he later became a Governor) and left there to study Medicine in 1939. However, he left in 1940 to join the Royal Navy and served throughout the war, culminating in being promoted to first lieutenant on T and U class submarines most notably on HMS Unseen, patrolling the Mediterranean whilst based in Malta (1943–1944).

Returning to the Medical School at Leeds in 1946 he graduated MB CHB in 1951 with honours, PhD in 1958 and was awarded the DSc in 1965. His lifelong commitment to his speciality was seen from his first appointment – as house officer in cardiology at Leeds General Infirmary and throughout his posts from demonstrator to professor. He sought to exploit the clinical applications and relevance of basic physiological sciences.

At the time of him joining Leeds Medical School, it already had a reputation for cardiovascular work in physiology, medicine and surgery and he was soon involved in this exciting and developing field. After his PhD he had a stimulating year as a research fellow at the National Heart Institute in Washington DC, teaming up with several of the best American workers on the heart. This year was to prove seminal. On his return to Leeds, Ron set out to create something similar at Leeds. The Cardiovascular Unit was formed, within the Department of Physiology, which combined responsibilities for clinical cardiac investigations with fundamental 'blue skies' research of the highest quality. In 1966 he was appointed to a Personal Chair and in 1977 to the headship of a separate Department of Cardiovascular Studies, his chair being endowed by the British Heart Foundation, one of the first to be endowed by the Foundation.

Loyal to his colleagues, and commanding loyalty in return, he founded a dynasty of Leeds-trained cardiovascular physiologists who have spread far and wide. The reputation of his department as a centre of excellence was due to his persistence in demanding high standards of performance not only from himself but also from his collaborators. He enthused his departmental staff by his style of work. The duration of the meticulously monitored experiments done in his laboratories was legendary, even among students.

He served on the editorial boards of several prestigious journals and was a member or chairman of several committees giving advice to government departments on physiological topics. He rendered valuable service to a number of high powered UK committees, notably the University Grants Committee, the British Heart Foundation and the Ministry of Defence.

Following retirement in 1985, he took up two six-month appointments at the newly formed medical school of the Chinese University of Hong Kong and also continued research collaboration with Gianni Losano at the University of Turin. He was awarded an honorary degree in Medicine and Surgery by the University of Turin in 1993.

Ron was a true Yorkshire man. He played cricket for Leeds University in his early years at Leeds and supported Yorkshire cricket, Leeds United and Leeds Rhinos. He was an amateur photographer, taking pictures mostly of his family and was very proud that he once won a prize for a photograph of his eldest granddaughter and her puppy awarded by the magazine, *Amateur Photographer*. He was an enthusiastic gardener and took particular pleasure in growing an immaculate lawn, camellias, roses and vegetables.

Ron Linden married Isobel Hendry in 1944 when stationed in Campbeltown, on the west coast of Scotland. They had only known each other for three weeks when they got married. Isobel died in 2007. They had three sons.

Roger Linden

Cecil Kidd writes:

Following the award of his PhD at Leeds, Ron spent a seminal year as a research fellow at the National Heart Institute at Bethesda, Washington DC, working with some of the best US workers in cardiovascular physiology, led by Sarnoff examining mechanisms of cardiac 'contractility' in the whole heart. On his return to Leeds he decided to set up a similar model there, initially funded by the Wellcome Trust.

The Cardiovascular Unit in the Department of Physiology was the result and it initially comprised three laboratories working on different aspects of cardiovascular physiology led by Ronald, John Ledsome and myself: Roger Hainsworth replaced John when he went to Vancouver. Roger focused on the physiology of the peripheral vascular system and I worked on the various cardiac receptor and central nervous mechanisms. Over time the Unit evolved, became a Department and eventually also had clinical staff and responsibilities: the overall aim was to pursue basic physiological science and to exploit their relevance to cardiac clinical applications.

Ron and his group of students produced a substantial series of studies that rigorously examined the influence of the various factors

affecting the force of contraction of cardiac ventricular muscle. Using the rate of change of left ventricular pressure (d*P*/d*T*) as an index, they were able to identify effects of autonomic nerves, heart rate and length etc. on the inotropic state of the left ventricle. The work introduced a significant rationalization of knowledge at the time which was bedevilled by non-specific terms such as 'contractility' and 'vigour' of contraction. The papers were published in *The Journal of Physiology* and the overall conclusions were adumbrated in a chapter he wrote with Mike Snow in *Recent Advances in Physiology*. He introduced new rigorous approaches and techniques in acute mammalian work including the maintenance of an appropriate acid–base balance, using the then new techniques for acute measurements in blood and gas chemistry such as pH, P_{O_2} and P_{CO_2}.

Ron then took up the topic that occupied him for the major part of his research career. He started an investigation into the role of right and left atrial receptors in control of blood volume. Several workers, including Henry and Gauer, had previously suggested that atrial receptors were involved in blood volume control but the provoking stimuli were unclear. Work with John Coleridge and Albert Hemingway in Leeds before he went to the States had examined the pattern of distribution of these mechanoreceptors in the canine heart following their initial description by Paintal. Ron and his group devised preparations in which the left atrial receptors could be selectively and discretely stimulated by inflation of small balloons, without affecting return of blood to the heart. They measured heart rate and urine flow. Each inflation was followed by an increase in heart rate and urine flow. Over a period, they examined the characteristics of the responses including the alterations in receptor activity following their specific stimuli. Later, he and his group, now including Kappagoda and Snow, devised preparations that could examine responses evoked by selective stimulation of right atrial receptors. Again, the responses included a similar increase in heart rate and urine flow to that evoked by the left atrial receptors. Overall there was little doubt that the evidence clearly indicated that the afferent sensory side of the responses involved vagal afferent fibres from receptors in the right and left atria.

They were also able to show that the increase in heart rate was due to increased activity in sympathetic efferent fibres to the heart but was without effect on cardiac vagal motor fibres. However, the nature of the efferent pathways involved in the increased urine flow following stimulation of the receptors was more controversial.

Ron celebrating his 90th birthday.

Direct recording of activity in sympathetic nerve fibres during left atrial receptor stimulation by the Leeds group demonstrated that there was an effect on activity in renal sympathetic fibres. This was decreased at a time when activity in efferent sympathetic fibres to the hind limbs and visceral abdominal areas was unaffected. In neural terms, the pattern of these efferent responses was very different from any other described at that time. However, there was also strong evidence from other labs that a humoral pathway, probably including antidiuretic hormone (ADH), was involved. Ron and his group followed this up with a series of studies. They devised an assay for plasma ADH and learnt how to destroy the pituitary gland, acutely, thus removing the source of ADH. An increase in urine flow still occurred when the receptors were stimulated when there was no increase in plasma ADH. For a time these experiments appeared to falsify the hypothesis that ADH was involved and the Leeds group examined the nature of a possible diuretic agent. An assay was then devised, using the malphigian tubule of the bed bug (*Rhodnius prolixis*) to show the presence of such a diuretic and that was unaffected by ADH. Further experiments were carried out and the conclusion was that atrial receptor stimulation resulted in release of a blood-borne diuretic agent in addition to ADH. At present, its nature is unknown as are the relative contributions of the reduction in neural traffic in renal sympathetic nerve fibres, the increase in the postulated diuretic agent and the reduction in plasma ADH to the increase in urine flow which follows stimulation of the atrial receptors. That is how the picture currently remains: many disagree with the idea of a diuretic agent but the experimental evidence says otherwise!.

Throughout his career, Ron was interested in exercise and was a strong informal advocate of the Canadian Air Force Programme; indeed over a beer (or two), he persuaded many of us to take it up. This exercise theme comes out in another of his projects but now in patients. This examined the relationship between changes in the electrocardiogram during exercise in patients with coronary heart disease and attempted to define the extent of the problem.

A novel exercise test was developed and was shown to provide an accurate index of myocardial ischaemia and its severity. It avoided maximal or excessive exercise, which could limit performance by means other than the onset of cardiac symptoms. Instead, a sub-maximal test was used to derive an index based on the progressive ST segment depression of the electrocardiogram, relative to an exercise-induced increase in heart rate. The steepest slope obtained in 13 electrocardiography leads was labelled as the maximal ST/HR slope. It was shown to be an accurate index of the presence and severity of myocardial ischaemia resulting from coronary heart disease and left ventricular enlargement.

This again demonstrates Ron's primary commitment throughout his career to the exploitation of the relevance of basic physiological science to clinical situations.

The Department of Cardiovascular Studies was unique in the UK at the time and was totally funded by the British Heart Foundation, Wellcome Trust and MRC.

Ron published many scientific papers and reviews in journals of the highest quality, including *The Journal of Physiology*. The Department hosted a number of very successful international conferences and took a leading part in the periodic visits of The Physiological Society to Leeds. With Tissa Kappagoda, he published a Physiological Society monograph entitled *Atrial Receptors*.

Ron served on the Editorial Board – and became Chairman – of *The Journal of Physiology* as well as other prestigious journals. He was Chairman of the Cardiovascular Commission of the International Union of Physiological Sciences for a number of years.

He became a Member of The Physiological Society in 1956, serving on the Committee from 1968–73. Following his great friend Robert Comline, he became Treasurer, the Senior Officer of The Society at the time, from 1980–86, after which he was elected Honorary Member.

In the Department and in every aspect of his career, Ron created an atmosphere characterised by a rigorous attention to detail and positive vigorous discussions with everyone: he generated a very relaxed atmosphere with frequent highly enjoyable and bibulous get-togethers and parties. There was constant positive critical debate and analysis allied to experimental confirmation: in the early days, ideas of Karl Popper were frequently invoked. He stimulated many young scientists from a wide range of backgrounds and countries to pursue high-flying careers in laboratory experimental work in physiology and its related areas of anaesthesia, surgery and cardiology, and the pharmaceutical industry.

We all owe him a huge debt. He had a remarkable ability to enthuse individuals of whatever background and to gain their trust and loyalty which he richly rewarded.

Note: in preparing this account, I had help from Roger Linden, Michael Snow, Peter Mcwlliam, David Mary and Ann Silver. I am very grateful for their assistance. Any omissions, errors or misinterpretations are solely my responsibility.

Margaret Hay Gladden

21 December 1940–3 April 2010

Margaret had a long and productive research career, spanning four decades, which she managed to combine with raising four children. She was born, an only child, in Lancashire, the daughter of an industrial chemist from whom she inherited an interest in designing equipment to solve or overcome laboratory problems.

She was also active outside science, being an international rower in her youth and later playing an organising role in the Quakers and being an active supporter of the Liberal Democrats, putting her interest in gardening to use by hosting fund-raising garden parties. She returned to Quakerism as it has been in a Welsh branch of her ancestry in earlier times, possibly during George Fox's lifetime. She was a delightful colleague and had a love of driving at high speeds, which could be alarming if you were driven by her, as she surfed traffic, whilst elaborating Quaker principles.

She was also a thoughtful feminist and deplored the tendency for scientific controversies to break out amongst her male colleagues (outside of Glasgow) so very quickly, preventing genuine scientific dialogue. As she regarded men as the weaker sex, she was invariably kind and encouraging to her younger male colleagues. Whilst active in spindle physiology, her work was informed throughout by her medical training and she was aware of the need for research to assist eventually in the care of patients.

After retirement, Margaret continued to pursue her research into the effects of opiate anaesthetics on the output of fusimotor axons with the same characteristic dedication. As well as working on spindle physiology, she latterly acquired an additional interest, prompted by her compassionate nature: she was currently exploring the role that spindle 'reset' might play in alleviating some of the symptoms of motor dysfunction. This involved work in schools putting a promising form of therapeutic massage on a more scientific basis, as a means of helping to improve motor function in children with cerebral palsy.

As Guy Bewick relates below, she was still planning experiments at the time of her death. Margaret published over 70 papers, mostly in *The Journal of Physiology* and almost entirely on the subject of muscle spindles, though with an occasional foray into Victorian medical education and the use of networked computers in physiology teaching. Before the tyranny of citation analysis took hold, the proceedings of symposia used to be highly regarded and Margaret co-edited the proceedings of three such symposia.

After qualifying in medicine from London University in 1965, simultaneously taking her MRCS and LRCP, she took a DCh, also from London, in 1968. She then transferred to Geoffrey Kidd's laboratory in Liverpool where she held a MRC junior research fellowship and from where she was to publish her first papers that set the theme for most of her subsequent research: the relationship between structure and function in the innervation of skeletal muscle, especially the spindle. Her thesis was on the development of innervation in tenotomised muscle in the rat, and she was awarded the degree of PhD by Liverpool University in 1971.

From Liverpool, Margaret moved to Glasgow, joining Ian Boyd's laboratory in the then Institute of Physiology as a research fellow and successively as lecturer (1973), senior lecturer (1983) and reader (1991). The early seventies was a time when the dual model of the

spindle was coming under increasing pressure from new observations in histochemistry, EM and physiology. This had been formulated by combining Peter Matthews' division of fusimotor actions into dynamic and static categories with Ian's nuclear bag and nuclear chain fibre systems. Despite being overthrown by the late seventies, the simplicity of the dual model might account for the sorry fact that it continues to be described in many current textbooks. Margaret's part in the overthrow began when she extended the late Sibyl Cooper's observations on the distribution of elastic fibres in spindles and showed that the prominent elastic fibres of the polar regions of spindles were concentrated around just one of the (usually) two nuclear bag fibres. This nuclear bag fibre, now known as the bag_2, was innervated by static fusimotor axons, whereas the bag fibre without such a concentration of elastic fibres was innervated by dynamic fusimotor axons and is now known as the bag_1 fibre. These results were obtained using a preparation of the tenuissimus muscle with intact nerve and blood supply that seems to have been introduced by Margaret to Ian's lab following her visit to Toulouse, where it was developed by Yves Laporte and the late Paul Bessou.

The recognition that there were not two, but three, types of intrafusal muscle fibre (bag_1, bag_2 and chain) focussed attention on the pattern of their motor innervation, especially the specifically fusimotor (γ) static axons. On the one hand it resolved the conundrum that dynamic axons always activated bag fibres whereas static axons might activate bag fibres or chain fibres, or both together; on the other it raised the question as to why the static axons needed two very different effectors. Together with Peter McWilliam, Margaret soon reported that bag_2 and chain fibres could, to some extent at least, be separately activated by cortical or midbrain stimulation. In her continuing work with Ian, until his untimely death in 1987, Margaret pursued the idea that there might be two, or even three, kinds of static γ axon. The idea was repeatedly criticised by David Barker's group in Durham and with further evidence against it from Yves Laporte's group, now in Paris, it appears that even before 1987 Margaret had her own doubts as she candidly related when she abandoned the idea in a review she presented at a symposium held in Glasgow in honour of Ian's memory as part of the IUPS congress in 1993.

In Glasgow in the early nineties, Margaret focused her attention on central and reflex activation of γ motoneurons, but she also developed an interest in the other sensory innervation of the spindle, the secondary endings supplied by group II afferents. Much of this work was carried out in collaboration with Yves Laporte's group. Her last major collaboration was with Elżbieta Jankowska of Göteburg on group II and interneuronal inputs to γ motoneurons; her last full paper to be published in *The Journal of Physiology* was in 2002 on coupling of Ia and II afferent output by static γ axons, so returning once again to the constant theme of the relationship between structure and function in the spindle.

Peter McWilliam writes:

I first met Margaret when I came to Glasgow in 1971. She had immense technical expertise and endless patience with all things at the micro level. She also had endless patience with people and with me in particular as I was always wanting to try new things in the lab. Although Ian was my formal PhD supervisor, his duties as head of department meant that I relied on Margaret for much of the day-to-day supervision. Our greatest piece of work together was working out the motor innervation of the mammalian muscle spindle. This involved developing a preparation where we could isolate and observe a single spindle under the microscope whilst maintaining its nerve and blood supply so that we could also isolate the multiple individual afferent and efferent axons to the spindle. The experiments would take 30–36 hours and involved us working in shifts.

Margaret and I eventually enjoyed a memorable eureka moment at about 5:00 am on a fine summer's morning when we suddenly realised exactly how the intrafusal fibres of a spindle were innervated by the static and dynamic γ motor fibres. In later years it was great to see our wiring diagram of the spindle reproduced in several text books.

Margaret always had tremendous energy and stamina for these long experiments which stemmed from her rowing. She competed at international level and I have memories of her taking time off to compete in the coxless pairs at the European Championships. One year she gave birth to her first child (a daughter, I think) midway through a series of long experiments. As I recall she completed an experiment about 48 hours before the baby was born despite the rest of us in the lab imploring her to take things easy. Mum and baby were back in the lab about a week later! She always had a smile and a kind word for all she met.

Guy Bewick writes:

I met Margaret through Bob Banks, at Durham University, a fellow muscle spindle physiologist. We all met previously at local and national meetings, but more particularly over the last 2–3 years. We invited Margaret to become a regular attender in our group discussions on an MRC project Bob and I are collaborating on. She took a very active part in proceedings, always looking so hale and healthy, and it was a great surprise to hear of her strokes. We greatly appreciated her contributions to our meetings, especially her enthusiasm and depth of knowledge in her field of research. Her wealth of experience was invaluable and she will be greatly missed both as a scientist and as a warm and generous colleague.

Margaret is survived by her former husband John Womersley and her children, Hugh, Gillian, Rona and Howard.

Robert M Banks, Michael Lucas, Jim Morrison and Ian McGrath with thanks to Peter Ellaway, Peter McWilliam and Guy Bewick

Richard Edwards

(1939–2009)

Professor Richard HT Edwards was a physiologist and clinician who had a major international reputation for his research into understanding the way that skeletal muscle obtains and uses energy to fuel contractions, in muscle damage and into the muscular dystrophies. He was also widely acknowledged to be a caring and diligent clinician, had huge energy, and was an inspiration and mentor to many junior colleagues.

Richard was born on 28 January 1939 in Llangollen, North Wales, a son of the local butcher and educated at LLangollen Grammar School. He studied Medicine at the Middlesex Hospital Medical School. He was reputed to have won almost every prize available to undergraduate medical students and intercalated in physiology gaining a first class honours. His initial research interest was in respiratory physiology and as a medical student he was able to combine this new enthusiasm with a great love for mountains when he undertook research into the effects of altitude on regulation of breathing at the Observatoire Vallot, the research station at ~4362 m on Mont Blanc.

On completion of his medical training, Richard was appointed to a position at the Hammersmith Hospital and Royal Postgraduate Medical School and began his interest in skeletal muscle that was to be the main theme of his research. This research was particularly stimulated by a sabbatical undertaken as a Wellcome Trust Swedish Research Fellow at the Karolinska Institute in 1970. He worked with Tor Sjostrand, Eric Hultman and Roger Harris, and during that time he learned the technique of needle muscle biopsy that was to shape his research career. This opened up the possibility of undertaking repeated sampling to study rapid changes in muscle composition in both healthy subjects and patients during exercise. On his return to the UK, he exploited this and published a series of landmark papers in *The*

Journal of Physiology, *Clinical Science* and *The Lancet* describing the changes in energy supply in muscles of subjects during exercise. The Hammersmith Hospital at that time was an ideal environment for this work and Richard worked closely with Professor David Hill (son of AV Hill, the 1922 Nobel Prize winner for Physiology) and Professor Victor Dubowitz in developing his studies in muscle and neuromuscular disorders. They secured a major grant from the Muscular Dystrophy Association of America to establish a Neuromuscular Centre with purpose-built laboratories, and attracted an outstanding research team that included Drs Archie Young, Caroline Sewry, David Jones and Jan Witkowski.

In 1976 Richard was appointed to the Chair of Human Metabolism at University College Hospital (UCH) to succeed Professor Charles Dent FRS.

Richard, in 1980, studying muscle metabolism in his own biceps muscle using 31-P NMR with an early Oxford Research Systems Instrument.

He was only 36 on appointment. Several of the research team from the Hammersmith moved with him and others such as Michael Rennie, Diane Newham, Mark Wiles, Kerry Mills and myself now began to work with him. The great strength of Richard Edwards was his ability to inspire and mentor his junior colleagues and all of us benefited greatly from working with him. UCH proved to be an immensely productive environment for this research. The group published important ground-breaking studies in muscle energetics, muscle protein turnover, muscle damage and muscle disorders. At that time, Richard also worked with Professor Doug Wilkie in innovative studies using the new technique of magnetic resonance spectroscopy for obtaining entirely non-invasive measurements of muscle energy metabolism.

Richard was promoted to the Head of the Department of Medicine at UCH in 1982, but in 1984 he became Head of the Department of Medicine at the University of Liverpool. Richard's 12 year old son, Tomos, had been tragically killed in a road accident in 1982 and the call of being near enough to the mountains of North Wales to live there had become very strong for Richard and his family. In Liverpool, he succeeded Professor David Price-Evans and he proceeded to revolutionise the Department of Medicine which increased dramatically in size during his time as Head. He also obtained funding to bring the first whole body magnetic resonance imaging and spectroscopy systems to Liverpool and worked with colleagues to introduce 'problem-based learning' (PBL) into the training of medical students. Richard had learned a great deal from Professor Moran Campbell about PBL as an innovative way of educating medical students to facilitate the life-long learning required by the profession, and together with Sir Robert Shields (Head of Surgery), Professor Michael Orme (Dean of Medicine), Drs Sam Leinster and Richard Griffiths, they restructured the Liverpool medical course to provide a model that eventually became adopted by other

UK medical schools. In Liverpool, Richard also mentored and brought another group of young colleagues into research on muscle including John Coakley, Phil Smith, Maria Stokes and Bob Cooper. At this stage, Richard also developed a major interest in the causes and alleviation of chronic fatigue syndrome (or ME) and developed exercise interventions to alleviate this condition that are still used today.

In 1996, Richard accepted an invitation to become the Professor of Research and Development for Health and Social Care at the University of Wales College of Medicine and Head of Research and Development for the NHS in Wales, based in Cardiff. This was a new departure for him, but was an influential position impacting on the direction of NHS-funded research undertaken in Wales. He eventually retired from that position in 1999.

On retirement, Richard put his enthusiasm and great energy into his home, garden and extensive woodlands in Nantmor, North Wales, a place where he was happy until his unexpected death following a cardiac arrest on 5 December 2009. He is survived by Eleri, his wife of 45 years, his daughter Rhiannon and grandchildren, William and Non. He will be remembered as a fantastically enthusiastic and energetic physiologist and clinician who was highly respected internationally and who inspired a generation of colleagues to work in this research area.

Malcolm J Jackson

School of Clinical Sciences, University of Liverpool

The Society also notes with regret the deaths of James Black, Johann Edge and Alastair Hosie.

James Black was awarded a Nobel Prize in 1985. He was elected a Member of The Physiological Society in 1962 and was made an Honorary Member in 1989.

Alastair became a Member in 2004.

Johann became a Member in 2007.

AD Bangham

(1922–2010)

Most academics believe earlier generations of scientists were more enthusiastic, and more eccentric about research than the present cohort. We can all reminisce about scientists who illustrate this statement, and for me the six decades of active science in Alec Bangham's life are a perfect example. Alec had a tremendous enthusiasm and genuine curiosity in his scientific career. He was always interested in big, important issues, and was prepared to enter new areas with radical and passionate ideas. Although the liposome must be his abiding memorial in research, he contributed in many other areas, including anaesthesia, lung surfactants, haemoglobin polymorphisms, water structure and the evolutionary origin of life. My first experience of his laboratory at Babraham was making surface charge measurements on single red cells using a very dilapidated microscope and electrophoresis chamber set into a grubby old aquarium as a waterbath, which nevertheless gave excellent results. Working in the lab allowed discussions on far-reaching and varied topics with Alec and his visitors, which was a true scientific pleasure.

The discovery that made Alec's lab a Mecca for visitors was the invention of the liposome (or smectic mesophase or bangosome) which offered a perfect experimental paradigm for the cell membrane. From his original EM observations with Bob Horne on hydrated lipid films, the lab developed a simple technique for making multilamellar, and later unilamellar lipid vesicles to be used in permeability and drug delivery studies in a vast number of applications. Protein incorporation was an obvious next step in mimicking cell membranes, and proteoliposomes remain a major tool for functional analysis of membrane transport. Immediate questions that could now be answered included the passive permeability

Alec with his iPhone.

of the cell lipid membrane to water, ions, important non-electrolytes (glucose, amino acids, urea) and lipid-soluble molecules. Manipulation of lipid composition (particularly cholesterol) and charge, saturation and chain length, defined the properties of pure lipid membranes, and lipid preferences of inserted proteins e.g. phosphatidylserine and phosphatidic acid supporting Na^+/K^+-ATPase activity added important information on annulus lipids.

Besides offering an ideal system for investigating the biophysical properties of the membrane, liposomes were developed as drug delivery systems, and with trapped haemoglobin as artificial red cells requiring several modifications of surface (adding polyethylene glycol) and size to avoid rapid removal from the circulation. The final use of liposomes that Alec learnt of whilst walking through the Beauty section of a local department store was in cosmetics. His approach to the elegant lady behind the counter saying '*You know, I invented liposomes*', led somewhat surprisingly to a VIP invitation to Paris to dine with the President of Christian Dior, an occasion he greatly enjoyed.

The mechanism of action of general anaesthetics was and remains a major topic for debate. Liposomes contributed to research in this area

initially by replacing the classical ancient olive oil–water partition as an index of hydrophobicity with a membrane-relevant parameter, and subsequently assessing effects of temperature and pressure on permeability changes in liposomes treated with relatively high doses of general anaesthetics. This led in 1976 to Bangham and Deamer proposing that anaesthetics might collapse the pH gradient across liposomes, and affect accumulation and release of charged neurotransmitters in vesicles. Coincidentally, Victor Whittaker working in an adjacent lab to Alec at Babraham, had just isolated synaptosomes, identifying the organelle for which the liposome was a model.

Babraham research on anaesthetics was not confined to pure lipid membranes. Experiments on goldfish behaviour were also pursued, and for a while Alec was excited by the fact that the Tubifex worms used to feed the goldfish also showed behavioural responses to anaesthetic alcohols, effectively eliminating the need for the fish. However, these experiments were interrupted by the supply of worms ceasing as the Thames became cleaner, and in spite of a false hope from Harrods' pet shop (who assured Alec they had Tubifex available but they turned out to be freeze-dried) work reverted to goldfish.

As every medical student knows, lung surfactant is lysolecithin and this was therefore an obvious topic of interest for a lipid enthusiast like Alec. He was able to identify the most effective solid phospholipids for this effect, and devise a delivery system to use phospholipid snuff to treat respiratory distress in premature babies.

Most recently, Alec's ideas became reminiscent of Susskind's Perfume in suggesting individuals have a 'fingerprint' of volatile organic molecules which are weakly ionized and both contribute to identity, but also alter surface charge on cells and affect immunological tolerance, a factor Alec considered might be important to the fetus.

Alec was renowned for his insightful but sometimes forceful comments, and for his party piece, a demonstration of the power of lipid monolayers. In this experiment he would set fire to a Langmuir trough full of water saturated with ether. As the flames rose he would add a phospholipid emulsion to the trough which spread as a surface monolayer and extinguished the flames. In a curious antithesis to Sydney Ringer's experiment, on one occasion his technician used very hard tap water to make the ether solution, resulting in the precipitation of the phospholipids as a calcium soap, and the flames persisting and getting bigger and bigger with no phospholipid effect.

Portrait by Humphrey Bangham.

Two wonderful examples of Alec's comments are first his question to Max Perutz after Alec had shown quite unexpectedly there were electrophoretic variants in horse haemoglobin, and Perutz had toiled for years on the X-ray structure of haemoglobin, to the effect 'Which haemoglobin are you studying?'; second on asking Robin Post what he was working on at the moment, and being given a recent reprint on the Na^+/K^+ pump, Alec noticed a major error in the abstract, which said K^+ was pumped out and Na^+ into cells, so he handed it back saying he understood it worked the other way around. However, occasionally comments were not so positive. After the Nobel prizewinner Arthur Kornberg spent three months in Alec's lab (and worked quite hard at the bench) his parting remark on leaving, and thanking Alec for his hospitality was 'I think there is a great future in membranes – for proteins'.

Alec set great store on family and friends. Those who worked with him were guaranteed a lifelong friendship, and I treasure the occasional letter with enclosed photographs and news of science and family I have received from him over the past thirty years. He was also as passionate over his hobbies (photography, sailing, gardening and Caucasian rugs) as his science and would lecture visitors enthusiastically on any or all of these.

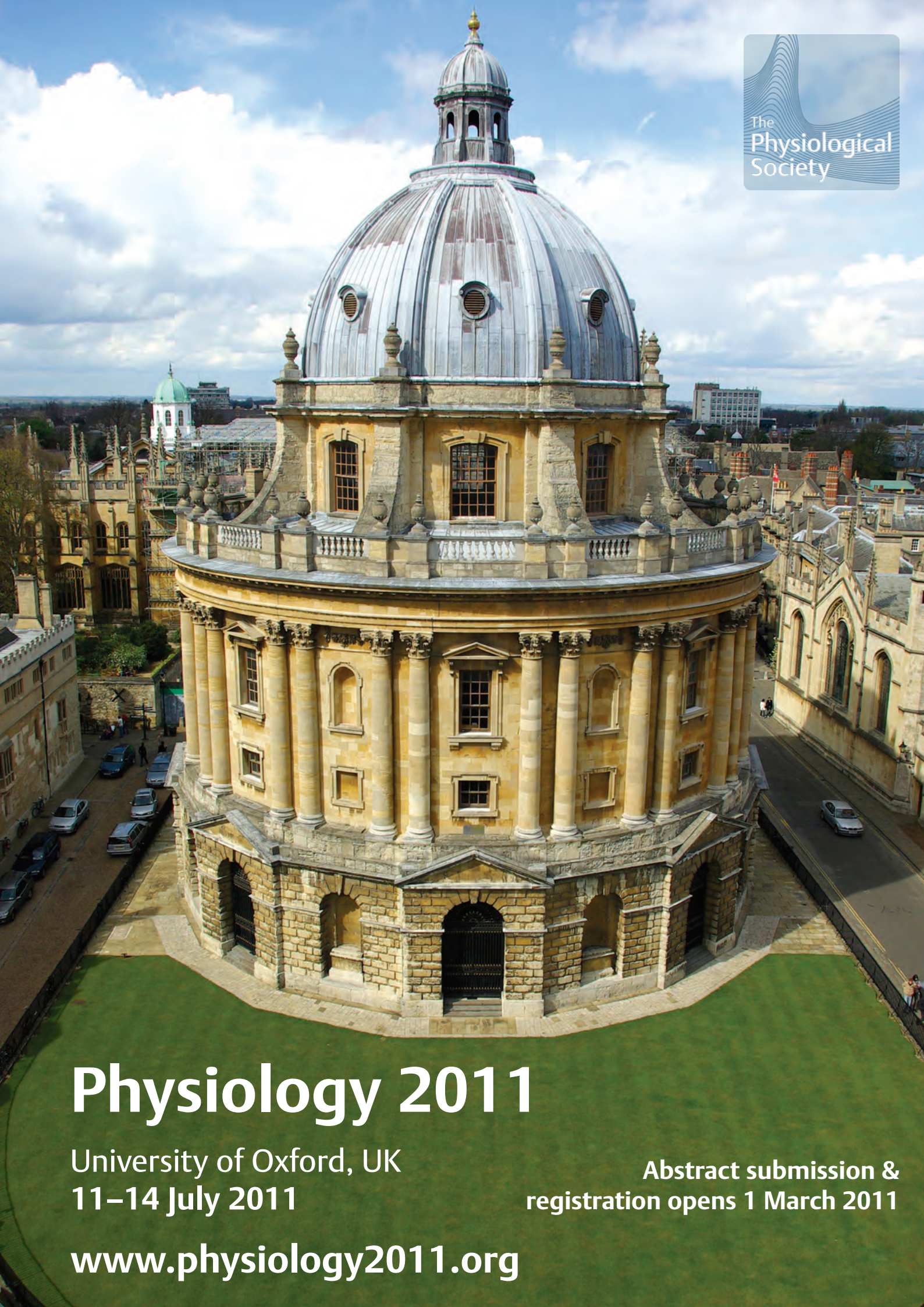
I regard it a privilege to have known Alec, whose enthusiasm, scientific courage and dare I say eccentricity, made him a scientific icon. He will be severely missed.

Clive Ellory

Deamer D & Bangham AD (1976). Large volume liposomes by an ether vaporization method. *Biochim Biophys Acta* **443**, 629–634.

Ann Silver adds:

Clive mentions cosmetics among the spin-offs from Alec's work. Others included the wonderful meringues that were a feature of Bangham hospitality: these solved the problem of what to do with the egg-whites left over from the production of lecithin from the yolks. Alec's Funeral Service, held outside in the Great Shelford Burial Ground, was taken by his one-time co-worker Martyn Hill. He recalled that Alec's response to the news he was going into the Church was 'Good, you can conduct my Funeral.' An apt (and cheering) feature of the Funeral was the blowing of bubbles – with typical Bangham imagination we were each given a bubble kit on arrival.



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Model of longitudinal splitting/shear-induced angiogenesis (p. 32).

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