PHYSIOLOGYNEWS

summer 2005 | number 59

Bristol Meeting
Images of Seville and the IUPS

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Two weeks in the life of ... a *Nature* Editor
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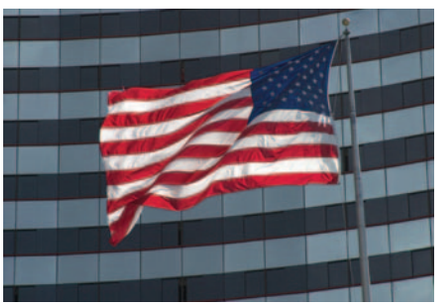
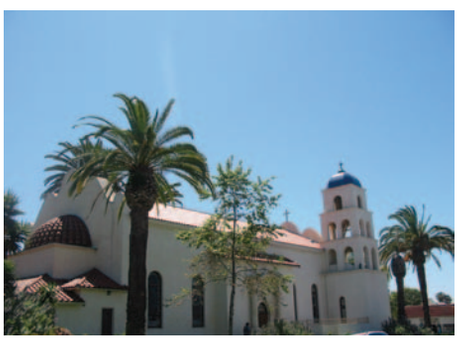
Appetite, the gut and obesity
Sir John Vane remembered

A publication of the Physiological Society

IUPS 2005

The XXXVth International Congress of Physiological Sciences *From genomes to functions* took place at the San Diego Convention Center from 31 March-5 April





Articles and more images from the IUPS appear on pages 10-12
(photos by John Hanrahan and Prem Kumar)

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

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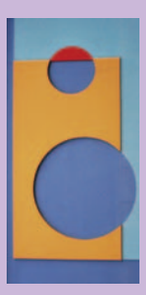

Cover illustration from *Physiology at Bristol*, p. 4

PHYSIOLOGYNEWS

Action points

Grants

For full information on Members' and Affiliates' Grants, Pfizer *in vivo* Physiology Grants, Network Interaction Grants, Non-Society Symposia Grants, Postgraduate Support Fund information and the Vacation Studentship Scheme visit: http://www.physoc.org/grants

Membership applications

Applications for Full and Affiliate Membership are received throughout the year and have no deadlines. A decision is normally made within 8-10 weeks of the Administration Office receiving the application. For full details please visit: http://www.physoc.org/join

Change of address

Members should inform the Administration Office of any changes of address, telephone, fax or email address.

Changes can be emailed to: jgould@physoc.org or updated online at http://www.physoc.org

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Physiology News

Deadlines

Letters and articles and all other contributions for inclusion in the Autumn 2005 issue, No. 60, should reach the Publications Office (lrimmer@physoc.org) by 9 June 2005. Short news items are encouraged and can usually be included as late copy if space permits.

Suggestions for articles

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

Physiology News Online

Physiology News is now available on our website: http://www.physoc.org.

Guidelines for contributors

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

Format of articles

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

Length of articles

This will be determined by the subject matter and agreed with the Editorial Administrator.

Submission of articles

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

Illustrations and authors' photographs

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

References

Authors are requested to keep the number of references to a minimum – preferably no more than two or three. Please cite all references in the style of *The Journal of Physiology* (see *Instructions to Authors 2005* at http://www.physoc.org)

In this issue

Usually when I write this column I try to spot a theme, or themes, in the issue.

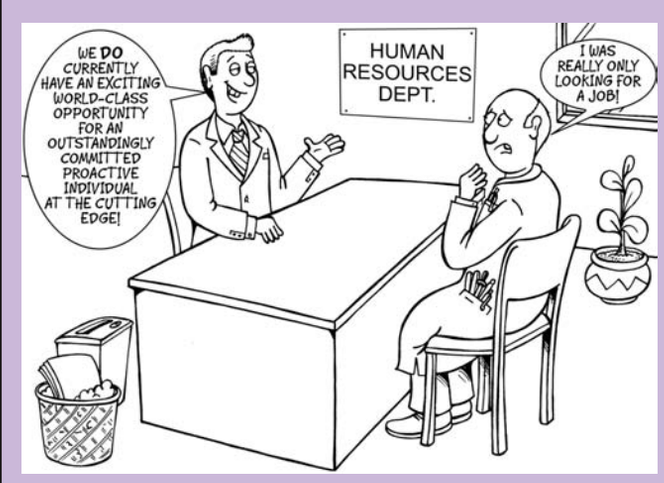
But this time, I can't see any. This *Physiology News* is defiantly without themes, intentional or unintentional.

For this issue, the watchword is 'variety'. Science articles and Society news. Meeting reports and previews. A letter from Australia, kicking off a new occasional 'Letter from ...' feature. Physiology and anatomy on TV. Physiology and art. Open access publishing. The diary. Ten key papers. Sir John Vane remembered. Mark Cain on the language of job adverts.

Editorial boards always aim to produce a journal, or magazine, with something in it to appeal to every reader. So variety is important to us. And, we hope, to you.

All in all, we're betting you won't miss the themes.

Austin Elliott



Unbelievable! (p. 49)

Hype and reality

I've always rather envied engineers. They build a bridge and then you can cross the river. There's no might or maybe about it. They must get their sums right, otherwise the bridge will fall down. And afterwards, there you are – you can now cross the river without getting your feet wet. What's more, it all happens on a satisfying human timescale of a few months or years depending on the size of the project. The engineers happily go off to their next project with the glow of a job well done, and life really has changed for anyone affected by the bridge.

Unfortunately, it's hardly ever like that in the biosciences. We deal with systems which are wet, messy and incredibly complex. They are often irreducible (at least in a way that leaves the main point of interest intact), and more often than not the redundancy of fully working systems means that they are difficult to control experimentally. What's more, the processes of evolution generally seem to have thrown biological systems together like monstrous Heath-Robinson machines, with no thought for economy, logic or the hapless experimenter trying to figure out what's going on.

So it's not really surprising that biosciences papers contain a lot of words like 'might', 'may' and 'could' in their conclusions, alongside phrases such as 'is not inconsistent with the idea that' and 'suggests that further work is indicated'. Interestingly, working out minute details has not been the difficult bit. If you look back 10 or 20 years, it's perfectly clear there has been really impressive progress across the board in elucidating details. The problem is the big picture. What does all this detail mean for the functioning organism? What use is any of this activity to society at large? Paradoxically, it seems that in the age of Big Bioscience, we get lots of data, but not that much useful new knowledge. Or at least, not that much useful new knowledge on a timescale of 3-5 years. So while our engineers are already busy building their third bridge and taking the plaudits, our poor bioscientist is yet again up against a grant deadline with just a handful of details and a lot of maybes and possiblys.

What are they to do? Well, predictably and blamelessly given the circumstances, they go in for claim inflation. They put the 'may' in front of a big enough statement to distract attention from the fact that the probability of the desired outcome ever actually happening is infinitesimally low. As in 'Further work in this area may thus result in a cure for Alzheimer's disease/cancer /cardiac arrhythmias/Hailey Hailey disease (or any other very rare and impressive-sounding disease that your reviewers won't have heard of).' This is obviously just part of the gameplay of modern bioscience and probably second nature to most readers of this magazine. You may have forgotten that you're doing it or even come to believe that your desired conclusion may really be possible. What of it?

Well, I believe that this professionally-driven conflation of hype and reality is harmful in at least three ways. Firstly, it encourages suspension of intellectual rigour within the biosciences. You may think that this doesn't matter, since it's only for the purpose of gameplay. But my experience is that far too many bioscientists do actually believe in and regularly restate possible outcomes which are quite clearly clinically, and even biologically, impossible. This does no-one any good. If subjects which are supposed to prize intellectual rigour are seen to suspend it for the key activity of disbursing funds, what message does this send to the outside world about the propriety of funding it in the first place? Secondly, extended gameplay has the unfortunate consequence that wildly optimistic suggestions and statements tend to reach the mass media very quickly. There was a time when scientists were held in high regard because 'breakthroughs' did often happen quite quickly after they were announced. But that golden age is long gone. Easy breakthroughs have been made and most of the rest don't look very likely. Part of the reason why scientists are now distrusted is because inappropriate professional pressures cause them to announce too many 'breakthroughs' that never actually happen.

A third reason why blurring hype and reality is counterproductive is because it obscures the main reason why we should be doing bioscience research in the first place. In my view this is not primarily because we expect our activities to cure cancer, dementia or whatever. Generally-speaking, most human conditions (apart from unavoidable old age) could be much more effectively dealt with by the entirely unglamorous activities of prevention. The main reason for our activities is cultural. Civilised societies like to understand the world about them and to appreciate its beauty. The justification for bioscience research in the 21st century surely is as much to do with aesthetics as with medicine. We should fund it for substantially the same reasons that we should fund art, sculpture or theatre. To state that this is obviously wrong because people don't understand or relate to bioscience is to identify a failing of the profession, not a refutation of the argument.

Perhaps you think that this is all nonsense. Or maybe you agree with some of the points. In the hope of stimulating a real debate on the issues raised here, *Physiology News* would like to hear from you. Do you have examples of the conflation of hype and reality? Have you been placed in a position where you have felt uncomfortable about making claims in writing that in reality you believed were at best unlikely (let us know anonymously if you wish)? Or do you believe that we will all live healthily to 500 years of age if only bioscience funding is increased? Do you agree that 21st century bioscience should be primarily a cultural activity? Or do you think that it is all about 'onward and upward' for medical progress? Send us your letters, articles and anecdotes.

These are questions that most of us don't spend much time thinking about. We should probably spend more.

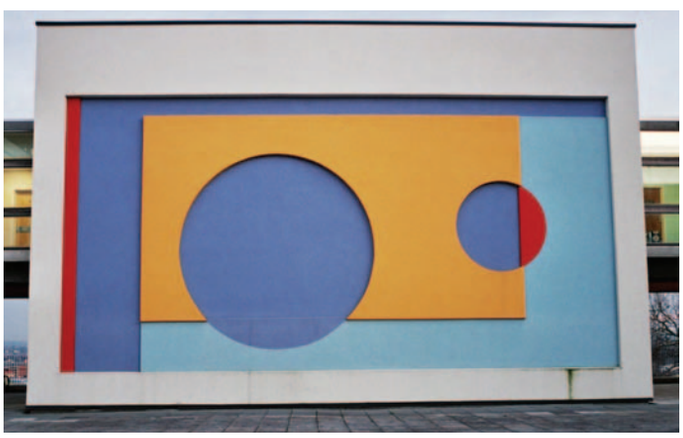
John A Lee

Physiology at Bristol

A warm welcome awaits delegates at the first of the new annual Meetings of the Society

The Department of Physiology is looking forward to welcoming the Physiological Society and the Federation of European Physiological Sciences (FEPS) to Bristol in July. This is the first of the new annual meetings that the Physiological Society has organised, and hence the largest ever to be held. The quantity and quality of science in Bristol during the week also promises to make it one of the most exciting. In the same week Bristol also hosts specialist meetings: preceding the Physiological Society/FEPS meeting are the Mammalian Myocardium 2005 and Young Physiologist symposia, as well as a series of workshops; following the meeting are a Physiology of Anion Transport symposium as well as two special symposia, on Sensorimotor Control and Dentinal Tubules, in honour of two recently retired members of the Bristol Physiology department: David Armstrong and Bruce Matthews.

The Department is housed in the School of Medical Sciences Building on University Walk, along with the Departments of Anatomy, Biochemistry, Pathology and Microbiology, and Pharmacology. Physiology has, however, undergone major changes since the Society last met in Bristol in 2001. Faculty reorganisation has placed the Department within the Faculty of Medical and Veterinary Sciences, and the Department has benefited from new building initiatives: the Medical Sciences Laboratory Teaching block, located behind the Medical Sciences Building and opened just before the last Physiological Society meeting in Bristol in 2001, provides high quality teaching space for undergraduate practical classes and has freed up much needed space for research; JIF and SRIF2 funding has subsequently enabled much of our research space and facilities to be renovated and upgraded.



A view of the University, with the Wills Memorial Building Tower in the foreground (top) and on campus (above). A view of Christ Church in Clifton Village, the Downs and Clifton Suspension Bridge (below).

The City of Bristol

The city of Bristol goes back to Saxon times, when it first developed at the junction of the rivers Avon and Frome. A bridge was built there and the settlement was known as Brigstow, which under the influence of the local dialect became Bristol. However Bristol's history has not always been one to be proud of: its prosperity boomed in the mid 18th century as a centre for the slave trade, and subsequently in the 19th century when the cigarette and tobacco manufacturers W. D. and H. O. Wills provided much of the city's prosperity. The Wills family was, however, a generous benefactor of the University, which started life as University College in 1876 and received its Charter in 1909, and paid for the University (Wills) Tower, which is a prominent landmark in the city and was completed in 1926. During the 19th Century the city became associated with the engineering achievements of Isambard Kingdom

Research in Bristol

Bristol physiology has retained its traditional strengths in *in vivo* and systems physiology, while incorporating molecular and genetic approaches into its work; research is buoyant, with current grant income at £7.5M. The Department has 22 academic staff, 11 research fellows, 20 postdoctoral researchers and 21 postgraduate students, supported by 28 technical and five secretarial staff. It has also been strengthened by a number of new appointments, with Paul Martin and Kate Nobes moving from UCL, Peter Brennan from Cambridge, Helen Kennedy from the University of Wisconsin-Madison, Matt Jones from MIT, who will shortly be taking up a UK research council fellowship in the Department, and Clive Orchard, who moved from Leeds to take over as Head of Department in February. As part of the Department's continued commitment to systems physiology we also run an annual intensive short course for undergraduates and postgraduates to obtain hands-on experience of *in vivo* research techniques. This is sponsored by the Physiological Society and the British Pharmacological Society, with funding from the Wellcome Trust and several major drug companies.

Current research in the Department is focussed on three main areas – Cardiovascular Sciences, Cell Biology, and Neuroscience - each of which forms a major part of the corresponding Faculty research themes.

Cardiovascular Sciences

Cardiovascular work in the Department falls into three main areas: cardiac muscle, microvascular physiology and control of the cardiovascular-respiratory system, with a shared interest in trying to understand the function of the cardiovascular system in health and disease.

Working on cardiac muscle, Jules Hancox continues to elucidate the function of the vitally important, but little understood, atrio-ventricular node and the basis and treatment of cardiac arrhythmias and, with Harry Witchel, uses mutagenesis to investigate structure-function relations of cardiac HERG K+ channels. Andy James' interests are the modulation of cardiac function by G-protein-coupled receptors, the mechanisms that underlie hypertension-associated atrial arrhythmias and, with Jules Hancox, sex differences in cardiac electrophysiology and the occurrence of arrhythmias. Clive Orchard investigates cardiac excitation-contraction-coupling and its regulation, in particular the role of the t-tubules, exploiting a novel technique developed in his laboratory that, for the first time, enables cardiac ventricular myocytes to be detubulated.

In microvascular physiology, Dave Bates, who holds a BHF lectureship, is pursuing his discovery of the role of store-independent transient receptor potential calcium channels in growth factor signalling in blood vessels, and the role of lymphatics and lymphangiogenesis in cancer metastasis. In collaboration with Steve Harper from the Academic Renal Unit at Southmead Hospital he is also extending their discovery of inhibitory VEGF splice variants, and together with Chris Neal, the renal team are investigating the role of the podocyte in regulating glomerular filtration. Phil Langton's interests focus on the regulation of smooth muscle excitability by the endothelium, by mechanical stresses and by local changes in ionic conditions.

Julian Paton, who holds a Professorial Research Fellowship, is investigating the role of the brainstem in the aetiology of hypertension, using a novel *in situ* arterially perfused preparation. Sergey Kasparov develops and uses novel viral vectors targeted to specific cellular populations and combines them with confocal imaging in brain slices to investigate brainstem mechanisms of cardiovascular control. Together Julian and Sergey are using viral gene transfer combined with radio-telemetry to investigate chronic effects of transgene expression in the brainstem on cardiovascular-respiratory control in health and disease. Tony Pickering, who has recently joined the Department as a Wellcome Trust Clinical Research Fellow, also collaborates with Julian, on the autonomic control of arterial pressure, and with Sergey on the use of viral vectors for studies of the role of spinal noradrenergic projections in pain.

Cell Biology

The focus of the Cell Biology group is the molecular dissection of cell motility and contractility, with a common interest in motor proteins that produce tension and movement.

K W Ranatunga uses sub-millisecond laser temperature-jumps to study contractile activation and force generation in skeletal muscle, and is investigating the relative roles of active and passive forces (such as those due to titin) while Gerald Offer, a molecular modeller who works closely with K W, has proposed a new model of the arrangement and temperature dependence of myosin heads in muscle thick filaments. David Woolley uses rapid cryofixation and EM to resolve the conformations of dynein arms during flagellar motion and studies flagellar kinematics using caged ATP; his group was the first to demonstrate dynamic torsions, microtubule-tip displacements and basal sliding in living flagella.

Other members of the cell biology have a shared interest in the regulation of the actin cytoskeleton via the Rho family of small GTPases. Paul Martin's group investigates cell and molecular aspects of wound healing and inflammation, using genetically tractable model systems (mouse, zebrafish and Drosophila); they compare the actin machineries that drive re-epithelialisation with those of embryonic morphogenesis. Kate Nobes, who holds an MRC Senior Research Fellowship, uses microinjection techniques to determine the mechanisms underlying the attractive and repulsive interactions between migrating cells, with a particular focus on EphR/ephrin regulation of the actin cytoskeleton. Dawn Davies (who holds a RNID Fellowship) investigates neuroblast migration and the cell:cell and cell:matrix interactions that appear fundamental to regeneration of otic epithelium, while David Sheppard and colleagues use high-resolution single-channel recording to investigate the structure and function of the cystic fibrosis transmembrane conductance regulator (CFTR) chloride channel with the aim of developing rational new therapies for cystic fibrosis and related diseases.

Neuroscience

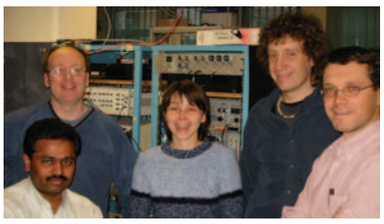
Bristol continues its traditional strength in sensory and sensorimotor neuroscience. The interests of individual labs range from molecular and cellular mechanisms involved in sensory transduction to supraspinal circuits controlling visceral and somatic behaviour. A particular strength is the combination of *in vivo* systems expertise with molecular techniques to gain insights into gene function.

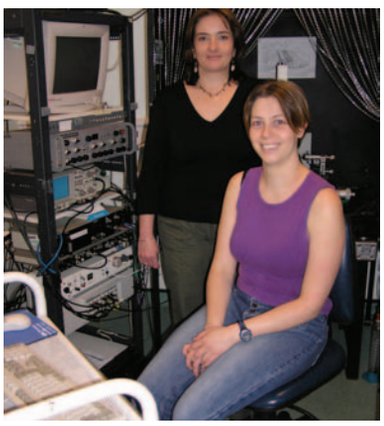
Helen Kennedy is interested in signal transduction by hair cells in the cochlea, studying calcium signal transduction in mammalian auditory hair cells using confocal microscopy. Her interest in the cochlea and hearing, a long-standing strength in Bristol, is shared with Dawn Davies (above) and Richard Helyer, who studies ion channel expression during mammalian cochlear development

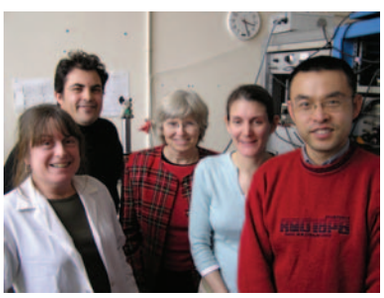
Bristol also continues to have a strong research interest in nociception. Sally Lawson characterises properties of nociceptive and low threshold mechanoreceptive primary afferent neurones and how these alter in chronic pain states *in vivo*, focussing particularly on ion channel expression, while Lucy Donaldson is studying the relationship between inflammation and nociception and the role of cyclooxygenase enzymes. Max Headley pursues *in vivo* studies of the role of excitatory amino acid transmission at the level of the dorsal horn in mediating nociceptor inputs, while Bridget Lumb is studying midbrain and hypothalamic circuits activated by nociceptive inputs, their contributions to descending modulation of spinal nociception *in vivo* and their possible role in co-ordinating active and passive coping strategies in response to different environmental challenges. Tony Pickering is interested in descending catecholaminergic control of dorsal horn processing of nociceptive inputs.

Richard Apps' research ranges from neural pathway tracing *in vivo* to the use of chronic neuronal recording from cerebellar circuits involved in sensorimotor control, with an emphasis on the regulation of voluntary movements. Peter Brennan studies the vomeronasal system and the action of pheromones on neural plasticity and mating behaviour *in vivo,* and Bob Meech is exploring the role of ion channels in simple neural and epithelial circuits *in vitro*, and how such systems combine to coordinate behaviour. Julian Paton and Sergey Kasparov (Cardiovascular, above), also form part of the Neuroscience group in Bristol.

Two Bristol neuroscientists retired in July 2004 after long and distinguished careers: David Armstrong and Bruce Matthews, although both are continuing their work as University Senior Research Fellows. In recognition of David's career and his work on supraspinal control of movement, especially by the cerebellum, and Bruce's career and his work on dental pain, two special symposia on these topics will take place on the Sunday following the meeting.







Vijay Pabbathi, Jules Hancox, Stephanie Choisy, Harry Witchel and Andy James share a laugh in the Cardiovascular Research Laboratories (top); Helen Kennedy and Lisa Grant (centre); Barbara Carruthers (left), Laiche Djouhri, Sally Lawson, Carol Berry and Xin Fang (above).

Aren't thermoregulation practicals fun! (above); Bridget Lumb's lab moving out for SRIF2 refurbishment (below): Barbara Carruthers (left), Frankie Semenenko, Lianne Leith Stella Koutsikou, Simon Lishman, Bridget Lumb (PS meeting secretary), Dave Gee and Dilys Parry.

Brunel, whose tradition lives on today in engineering associated with the aerospace industry. The city of Bristol is today also known for its beautiful Georgian architecture, historic harbour area and the legacy of Brunel, which is still much in evidence, as well as for its lively restaurants, clubs and pubs and arts scene and, of course, for the excellence of its University!

For those who wish to stay longer, Bristol is close to the historic city of Bath, famous as a Roman spa and as a fashionable Regency town, and its associations with many well known characters, including Jane Austen.

We hope that this taster of Bristol, and the science on offer in the Department and at the meeting, will encourage you to come to Bristol in July: we very much look forward to welcoming you here.

Clive H Orchard
Department of Physiology, University of Bristol, UK

Physiology practical class (right, top); Judy Harris uses a student to demonstrate how the CETL manikins will work (right, bottom. *Photo by Martin Chainey*)

Further information about Bristol, the Department and the meetings can be found at the following websites:

Bristol: http://www.visitbristol.co.uk/

Department of Physiology: http://www.bris.ac.uk/Depts/Physiology

Physiological Society/FEPS Meeting (including travel): http://meetings.physoc.org/bristol/

Mammalian Myocardium Meeting: http://www.bristol.ac.uk/mm2005/

Physiology of Anion Transport Meeting: http://meetings.physoc.org/bristol/cchannels.asp

Teaching in Bristol

The Department is proud of its tradition of high quality undergraduate teaching which was recognised by a score of 24/24 in the last QAA exercise. We run BSc degree programmes in Physiology and (with colleagues in Anatomy) Neuroscience, and teach Physiology not only to these students but also to BSc students taking degrees in related disciplines, as well as making significant contributions to the teaching of Dental, Medical and Veterinary students.

Our teaching involves all staff but much of the responsibility for course development and administration rests with a smaller group of individuals with Judy Harris, Eugene Lloyd, Frankie Semenenko and Phil Langton having particularly significant roles. Our teaching is also supported by 5 Medical Demonstrators, who provide excellent tutorials and teaching in practical classes.

Recent increases in student numbers - particularly medical - mean that we now teach around 1,200 undergraduates each year. This has led us to rationalise our teaching and assessment practices in ways that enable us to provide less labour-intensive, but still high quality, courses. For example, some small group tutorials and 'wet' practical classes have been replaced by interactive computer-based sessions and most of our exams, apart from final year BSc papers, are now in a format that can be largely machine-marked.

We were very pleased to hear at the end of last year that Bristol's bid to HEFCE for a Centre for Excellence in Teaching and Learning (CETL) focused on medical science teaching, and led by Physiology and Anatomy, had been successful. The initiatives within the CETL focus on practical teaching and are underpinned by funding of around £4.5M over a 5-year period, with about half of this coming to Physiology. This will enable us to develop projects that incorporate sophisticated computer-controlled 'human patient simulators' or 'manikins' into our physiology practical teaching and to create a web-based archive of digitised histological images that will be used in our histology teaching (Bristol is unusual in that most histology teaching is carried out by the Physiology Department).

Young physiologists in Seville

On the flight back to London after the Seville Young Physiologists' Symposium I ponder over the whole affair and am convinced that everything went so smoothly consequent to a series of fortuitous coincidences. For example, we had 20 posters on display and I had arranged for one of the local organisers to judge them to identify which should receive a 50 Euro prize. The academic in question vanished at some point during the afternoon and I never saw him again. Luckily, one of our guest speakers (who had already sat through and judged the oral presentations), Patrick Harrison of University College Cork, had most diligently worked his way round the posters and so stepped in as last minute poster judge.

The prize for best oral communication went to Salome Antolin of the University of Cambridge, and that for best poster communication was awarded to Nancy Mora of Valencia University, Spain.

As neither I, nor my two co-organisers, Consuelo Borràs and Mari-Carmen Gomez, had any knowledge of Seville, the venue for the YPS dinner had been booked by a woman from the travel agency that was acting as conference secretariat. Despite several pleading emails, she declined to tell us the name or location of the restaurant. Upon reading a notice that said that transport had been arranged from the conference centre to 'Alcazar de Sevilla', I mistakenly assumed that this must be the name of the elusive dinner venue. Some of the Spanish participants asked us whether this was the same place as the main meeting reception 'Reales Alcazares', so I grabbed Mari-Carmen and off we went to find out. Lucky that we did, because our restaurant was actually called 'El Cabildo' and 'Alcazar de Sevilla' is a royal palace and tourist attraction! Phew, another near disaster avoided.

Not everything went exactly to plan – there were some minor hitches during the day. The conference room was locked when we arrived but Consuelo managed to locate a key fairly swiftly. No PC was provided, but fortunately Mari-Carmen had brought her laptop. There was no technical support and we couldn't find the power switch to the projector, but I eventually found a man who did. Still, the speakers had obviously put much effort into their talks. The chairpersons had evidently read their abstracts and were well-prepared. The guest lectures were really enjoyable and the poster sessions were interactive, each author giving a two-minute summary of their poster in turn. And the rest, well it was down to serendipity…

Top (left to right): Ling Gao, Patricia de Winter and Consuelo Borràs.

Centre (left to right): Co-organiser Consuelo Borràs (Valencia), Nuria Matesanz (Madrid) and Anila Anwar, Francois Li, Ling Gao, Christina Warboys and Iya Goubareva (King's College London).

Above (left to right): Francois Li, Nuria Matesanz, Christina Warboys, Carmen Castillo Robles, Miriam Granado, Maria Miana and David Sanz Rosa

Patricia de Winter
King's College London, UK

Artery resistance and structure

The Physiological Society sponsored symposium *New aspects of artery resistance and structure* took place at 9 a.m. on the Sunday of the Seville Meeting. Suspicions of timetabling complications were raised by the posting of 9 p.m. on Saturday for the Gala Dinner, this being unfeasibly early for dinner in Spain. Honour was satisfied when this turned out to be the time that the buses planned to leave the hotels for the out of town location, so there was adequate time for a 4 hour sleep for those who planned to dine and attend the symposium. We did not record how many of the starting audience were counted in this number, but none of the speakers were.

The theme of the symposium was the need to consider the interaction between different components of the vascular wall in maintaining the structure of a blood vessel. The four speakers tackled topics ranging across the different cell types, their interactions and the signalling cascades involved.

Rhian Touyz (Clinical Research Institute, Montreal) set the scene with a beautiful presentation of the *Intracellular mechanisms involved in vascular remodelling in hypertension*. The signalling pathways in arterial smooth muscle cells were elucidated using a range of data from biochemical analysis to confocal images of the distribution of key signalling molecules. She described her lab's work in elucidating Ang II-mediated signalling in vascular smooth muscle cells, but pointed out that we still know little about specific molecules underlying aberrant signalling in hypertension or at what level some cascades become more important than others. She proposed that c-Src is a putative candidate because it is rapidly activated by Ang II and because it is a common upstream modulator to multiple Ang II-stimulated signaling pathways. Targeting such molecules/pathways could prevent or regress hypertensive vascular damage thereby ameliorating development of

hypertension and preventing target organ damage.

The theme of mechanisms involved in the damage done to vessels by hypertension was continued by Ana Fortuño (Cardiovascular Pathophysiology, Pamplona), who addressed the topic of *Oxidative stress and vascular remodelling*. Her theme was that oxidative stress plays an important role in the pathophysiology of vascular diseases, and that increased production of reactive oxygen species, mainly superoxide anion, contributes to oxidative stress and is implicated in pathological processes in the vessel wall, including endothelial dysfunction, activation of matrix metalloproteinases, and smooth muscle cells migration, growth and apoptosis. She described studies showing that NADPH oxidase is the most important source of superoxide anion in phagocytic and vascular cells. She elegantly described how its enhanced generation of superoxide is an important feature in several cardiovascular diseases, including hypertension, atherosclerosis and diabetes mellitus and went on to relate this to vascular remodelling.

The importance of extracellular structures in maintaining the function of arteries was then addressed by the symposium co-chair, Silvia Arribas (Department of Physiology, Autonomous University of Madrid), who described *Elastin's influence on small artery structure.* She described how studies in patients with elastin gene defects and knock-out mice have highlighted the importance of elastin in vascular morphogenesis and hypothesised that it might also be critical in vascular remodelling in diseases related to haemodynamic stress. She showed evidence for the importance of elastin for small artery structure and mechanics and described studies in the spontaneously hypertensive rat, a rat model of essential hypertension, indicating that elastin has a quite different organization from normotensive controls, having an internal elastic lamina with smaller fenestrae. Enzymatic digestion of elastin highlighted its importance in maintaining the 'remodelled' structure in hypertension and studies across the life course showed that the elastin 'defect' is an early feature in hypertensives. She highlighted the importance of elastin in the maintenance of normal structure in small arteries, in addition to its better known role in large vessels, and suggested that early alterations in elastin might be a key event in the process of inward remodelling in hypertension.

The meeting was rounded off by the other co-chair, Ian McGrath (University of Glasgow), who summarised the *New aspects of vascular remodelling: the involvement of all vascular cell types*. His thesis was that knowledge of vascular structures is largely based on an out-of-date, static view from two-dimensional histology that focuses predominantly on the tunica media with its close-packed smooth muscle cells and extracellular matrix. However, we now know that the adventitia and endothelium are key players in vascular growth and repair and this provides a new dynamic picture of blood vessels in a constant state of self-maintenance. He also showed confocal images of α and β adrenoceptor distribution in the types of resistance artery employed in remodelling studies and proposed that these, along with receptors for other vasoactive hormones, may be as important for modulation of vascular structure as for acute constrictor or dilator actions.

By the end of the symposium the audience had been swollen by those requiring more sleep than had been allowed for, and the occasion was generally considered to have been worthwhile.

In true Phys Soc tradition the speakers then set off for a very pleasant lunch, in compensation for the loss of the Gala, and resolved to deliver their manuscripts for timely publication – which they subsequently did. The papers will be available online May/June and published in the July issue of *Experimental Physiology*.

Ian McGrath
Institute of Biomedical and Life Sciences, University of Glasgow, UK

Students' views on the Seville workshop (see report on p. 9) ...

It was great to hear some of the founders of these [patch clamp] techniques explain them to us. The last day focused on ion channels and disease. Everything from uterine smooth muscle to cancer and neurodegenerative conditions was covered here, reminding us of how fundamental ion channels are to so many physiological processes. The poster sessions and lab tours were a great opportunity to get to know some other young researchers working on ion channels from all over Europe and the Ukraine and Russia. The Spanish hosts were particularly friendly and generous with their time showing us around their labs and demonstrating a wide range of techniques. Who can forget the wonderful dinner with wine and flamenco dancing that was laid on for us on the second night? I'd certainly recommend this workshop to any PhD students or post-docs working in an ion channel-related area. It gave an invaluable opportunity to put some faces to famous names in the field and to ask them questions in a friendly relaxed atmosphere. The talks were clear and informative covering a diverse range of topics and providing a great overview of the things that go on in ion channel research.

Jackie Kidd (*UK*)

As a student attending this course the broad range of seminars provided me with a basic knowledge on the history of ion channel discovery and the function of these channels in the intact tissue. The new ideas and use of techniques discussed in these seminars I feel will shape my own research in the future.

Katharine Dibb (*UK*)

I thought the workshop was a unique opportunity to meet people working in similar fields with common interests. The calibre of the speakers was excellent and I learned a fair amount of new science from them. The general feeling I got was that it was a friendly and relaxed meeting and the organisers made me feel very welcome.

Stuart Cain (*UK*)

All was wonderful: the place, the country, the city, the weather, the participants, the best professors in neurobiology and physiology, the lectures... Was a very good time to meet people and to discuss about life and science. Thanks a lot for all that the Physiological Society does for us.

Nicoleta Neacsu (*Romania*)

Ion channels: from physiology to pathology

A Physiological Society international workshop held at the Laboratorio de Investigaciones Biomédicas, Hospital Universitario Virgen del Rocío and Departamento de Fisiología Médica y Biofísica, Universidad de Sevilla from 7-9 February 2005.

The 8th International Society Workshop for young physiologists dedicated to ion channels was organised by José López-Barneo, David Eisner and Alex Verkhratsky. This was the first workshop in our traditional series fully open to all students regardless of their country of residence, rather then being specifically focused on Eastern Europe.

All in all the organizing committee selected 42 young scientists from more than 120 applications; the selection was based on the field of interest, scientific achievements and abstracts submitted. The participants came from 13 different countries: Argentina (1), Chile (1), Finland (1), Greece (1), Kenya (1), Poland (2), Romania (4), Russia (3), Slovak Republic (3), Spain (10), Thailand (1), UK (12), Ukraine (2).

The workshop commenced with welcoming remarks by International Secretary David Eisner and Jose Lopez-Barneo. The morning sessions consisted, as usual, of lectures given by an outstanding collection of speakers. In order of appearance these were Oleg Kristal (Ukraine), Erwin Neher and Peter Seeburg (Germany), Francisco Bezanilla (USA), Olaf Pongs and Arthur Konnerth (Germany), Emilio Carbone (Italy), Juan Lerma (Spain), Walter Stuemer (Germany), Susan Wray (UK), Bernd Nilius and Karen Sipido (Belgium) and Chris Peers

Above: Giralda, the tower of Sevilla Dome

Below: International Secretary David Eisner enjoys an evening at a country winery

(UK). The opening session presented a fascinating story of the uncovering of ion channels and the development of the patch clamp technique, and laid the foundation for later lectures dedicated to more specific aspects of ion channel physiology and channelopathies.

Lectures were followed with practical demonstrations* led by a very dedicated team of members of the host laboratory – Juan Ureña, Patricia Ortega-Sáenz, Jose Piruat, Konstantin Levitsky and Antonio Castellano – whose efforts deserve the highest appreciation.

Parallel poster sessions allowed close interactions between lecturers and students. These sessions were very stimulating and the overall standard of presentations was very high. A small evaluation committee picked the three best posters and the winners gave 10 minute oral presentations at the beginning of the last session. The winners, who also received Physiological Society certificates and a small cash award, were Natalia Sanchez-Soriano (Manchester University, UK), Alexandru Babes (University of Bucharest, Romania) and Annika Malkia (Finland).

On the social side of the meeting, the most memorable event was an evening in a country *bodega* (winery). Marvellous *jamon* and *manzanilla* (local ham and dry sherry) were followed by several courses of local specialities and the evening was crowned by flamenco dancing, which further increased the general euphoria.

Overall the meeting was yet another success (see box on p. 8 for some student feedback), for which the Society and all participants and lecturers are very much indebted to the local organisers, led by José López-Barneo.

José López-Barneo
David Eisner
Alex Verkhratsky

*The full list of practical demonstrations is available at http://www.physoc.org/international/seville2005/programme.asp#lab)

Society Lectures 2005

The Society has announced recipients of 2005 Prize Lectures as follows:

Annual Review Prize Lecture
Graham J Dockray (Liverpool)

G L Brown Prize Lecture
Godfrey L Smith (Glasgow)

Sharpey-Schafer Lecture
Neville H McClenaghan (Ulster)

The Paton Prize Lecture
John H Coote (Birmingham)
Landmarks in understanding central control of heart and circulation

Inaugural Annual FEPS Lecture
Alex Verkhratsky (Manchester)
Physiology and pathophysiology of the calcium store in the endoplasmic reticulum of neural cells

Michael de Burgh Daly Lecture
James F X Jones (Dublin)
Vagal control of the heart

Society Monographs

The Publications Office would like to hear from any Members who have spare copies of any of the Society's Monographs series for the archives.

IUPS 2005

The occasion of the IUPS meeting, held in San Diego from 31 March-5 April, provides an ideal time to update Members on current international activities of the Society

IUPS 2013

The Physiological Society submitted a bid to hold the 2013 IUPS congress, as did the national physiological societies of Austria, the Czech Republic and China. All four societies made their bids to the IUPS Council on 30 March and to the General Assembly on the 31 March. Following the presentations to the General Assembly a vote was taken and the UK bid was selected for 2013. The meeting is planned to take place in Birmingham in July 2013 and much work will be required in the intervening period. A steering group consisting of David Eisner, Bridget Lumb, Ian MacGrath, Alan North and Jeremy Ward has been established to organise planning for the meeting. This group is made up of members of the current Executive Committee of the Society. However, as the composition of the Executive changes over the next few years, this will no longer be the case. It has therefore been decided in future to include an additional three people in the group to represent the Executive at any one time. One of these would be the Treasurer. This arrangement will provide continuity of organisation while keeping the Congress organisation (and finances) firmly linked to the Society.

Although 2013 seems a long way in the future, organising IUPS will involve an enormous amount of work. The members of the steering group would welcome input and advice from Members.

Links with China

Members will be aware of the increasing investment in science in China. There are also large numbers of young Chinese scientists wishing to

New Council Affiliate representative Helen Taylor reflects on her first IUPS meeting

As a young PhD student at the University of Sheffield, the IUPS in San Diego was my first big meeting and I did not know what to expect. First impressions were good – the size of the convention centre, the organisation and security, and the efficiency of registration. In many cases those seminars which were relevant to my PhD seemed to overlap. I talked to a number of fellow UK academics and students who felt the same.

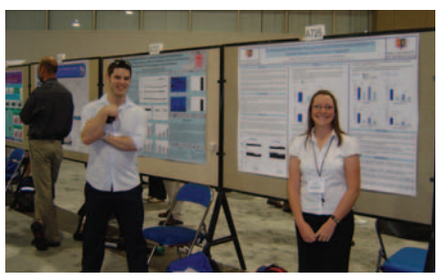
The Carl W Gottschalk Distinguished Lectureship of the APS Renal Section by Soren Neilsen was particularly good. Held in one of the biggest lecture theatres in the building, it attracted a large audience. Neilsen's work on the aquaporin AQP_2 (one of the membrane proteins that allow water to pass through the lipid bilayer) in the kidney was inspirational and, even though I am studying different membrane proteins, his work on the regulation of the aquaporin AQP_2 and the approaches he uses could transfer well to my research. The seminars were often full which made it exciting for a young physiologist.

I attended the poster sessions in the main hall, including my own, on three occasions and felt all were very successful. Many people attended each session and the informality made young physiologists relaxed. The one thing I felt most impressed with was the quality of the science.

The city was spectacular, and a perfect place to hold a conference of such a scale. There were many restaurants and bars nearby, and the seaport village was only a 10 minute walk away, which was a perfect way to relax during the intervals. San Diego had a lot more to offer, including the zoo, wild animal park and sea world.

Helen Taylor
University of Sheffield

Images of the IUPS



From the top:
1 San Diego Convention Center, IUPS venue
2 Birmingham students at the poster session
3 Flamingos preparing for *The Journal of Physiology* Symposium on PDZ domain scaffolding proteins
4 *Journal of Physiology* Editors Geraldine Clough and Steven Mifflin
5 Society Managing Editor Carol Huxley (left) with *Journal of Physiology* Editors Brian Robertson, Stefano Vicini and Chris McBain relaxing after the Editorial Board meeting at the W Hotel

(photos courtesy of John Hanrahan, Prem Kumar, Brian Robertson and Ann Watson)

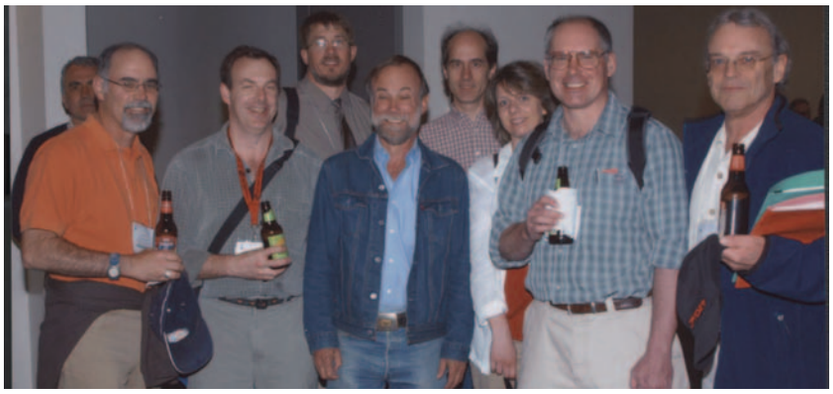
work in Members' laboratories as either PhD students or postdocs. There is considerable enthusiasm amongst members of the International Subcommittee to build closer links with China. This process has begun with a visit to China by Giovanni Mann (Chair of the Executive) and been facilitated with Ming Lei (Oxford) joining the International Subcommittee. Members of the Executive met with Tai Yao, Xiao-Min Wang and Zihe Rao from China at San Diego and it has been agreed that there will be a joint scientific meeting to be held in China (probably in Beijing in 2008). The same Chinese representatives will be present at the Bristol Meeting to continue discussions.

Capacity building in Africa

At the IUPS we were approached by two members of the IUPS Council for assistance with an initiative to help physiology teachers and lecturers in Africa, by organising teaching workshops. The IUPS itself has inadequate funds to support this project and has therefore approached the Physiological Society (as the largest European Society) for help. We would be grateful if any Members with an interest in helping in this area would contact either Helen Close or David Eisner.

Interactions with the American Physiological Society

Many active members of the Physiological Society regularly attend scientific meetings in the USA, and US physiologists often come to UK meetings. To date, however, there has been little formal interaction between the two Societies. In order to address this, representatives of the Physiological Society's Executive met with their counterparts from the American Physiological Society. We had a very constructive meeting and discussed issues such as a joint meeting (possibly in 2008), regular sponsorship of symposia at each other's meetings and beneficial registration rates for members of each society at meetings of the other. Finally, we also discussed combining our efforts in interactions with other regions. Examples included China and South America. Members of our Executive left with very positive views of future interactions.



Top (from the left): Douglas Bovell, Kirk Hamilton, Roger Worrell, Bruce Schultz, Paul Quinton, Dan Halm, Annick Guyot, John Hanrhan and Simon Lewis
Above: Yoshihiro Kubo (left) and Jack Feldman
Left: Quentin Pittman

International workshops

For several years the Society has organised workshops for young physiologists. Plans are under way for workshops to be held in Kiev, provisionally entitled *The study of nociception: from periphery to brainstem* co-organised by Bridget Lumb and Anne King (UK) and Oleg Kristal (Ukraine) and Sergei Khasabov (USA). We are also planning to hold a workshop in Prague in September 2006 provisionally entitled *Lung function in health and disease* co-organised by Jeremy Ward and Sergey Smirnov (UK) and Vaclav Hampl and Jan Herget (Czech Republic). Until recently, all but one of these workshops has been held in the eastern part of Europe in order to make them accessible to scientists from the former Soviet Union and neighbouring countries. (The exception was the workshop on **Ion channels** organised by José López-Barneo and Alex Verkhratsky held in Seville in February 2005). Teresa Tiffert and David Eisner are now planning (together with Fabian Michelangeli and Reinaldo DiPolo) a workshop on nerve and muscle to be held in Caracas, Venezuela.

Joint international meetings

Several meetings are being organised. A joint meeting with the Brazilian Society will begin on 26 August 2006. There will be a tripartite meeting together with the Slovak Physiological Society and FEPS to be held in Bratislava from 10-14 September 2007. We hope that as many Society Members as possible will be able to attend both these meetings.

Helen Close (hclose@physoc.org)
David Eisner (eisner@man.ac.uk)

In the next issue of *Physiology News*, *A week in the life of ... the IUPS*

A Physiological Society sponsored symposium, *Ion channels, genes and regulation in smooth muscle*, to recognise the contribution of Tom Bolton and Alison Brading will take place in the Department of Pharmacology, University of Oxford, UK from 5-7 September.

The proceedings of the symposium will be published as a themed issue of *The Journal of Physiology* early in 2006.

Cardiac electrophysiology

An IUPS Satellite meeting on *Mechanisms for maintaining intracellular Na^+ and Ca^{2+} homeostasis in the mammalian heart: implications for ischemia and left ventricular dysfunction* was held in La Jolla, CA, USA on 29-31 March 2005.

Amongst the numerous satellite meetings held around the IUPS 2005, there was a small focused meeting on cardiac electrophysiology, held at the Torrey Pines Hilton. The meeting organiser, Wayne Giles, invited a host of eminent speakers from around the world to address the current issues surrounding the mechanisms that regulate Na^+ and Ca^{2+} in the heart. This very brief report summarises only a few of the many subjects that were covered. The meeting began with a keynote address by Denis Noble (Oxford) entitled *Cardiac electrophysiology: from Hodgkin-Huxley to the physiome*. Denis gave an impressive account of the historical background related to the development of the mathematical models being used to investigate the role of ion transport mechanisms involved in the cardiac action potential. His address outlined the pivotal role of computing power, and in particular its accelerated growth, in the evolution of new models used to describe experimental data. He also described how models, much like practical experimental work, evolve over time and how modelling also has pit-falls that can all too often result in failure.

The main theme of the meeting was undoubtedly the Na^+ current (I_{Na}), and, in particular, the late (or the sustained) I_{Na} that remains active during the plateau phase of the action potential. One of the first few speakers (Jonathan Makielski, Madison) described properties of the human Na^+ channel and the implications for Na^+ loading in the event that late I_{Na} is increased. The existence of this I_{Na} means that Na^+ entry could occur even after the classical fast voltage-gated I_{Na} (responsible for the rapid upstroke of the action potential) has been inactivated. A number of the speakers

Top: David Fedida (University of British Columbia, Vancouver) talking with Denis Noble.
Centre: Jonathan Lederer (University of Maryland, Baltimore), left, and Peter Light, right, two of the speakers at the meeting.
Above: Busy poster session at the end of the day.
Below: La Jolla, satellite venue

provided evidence to show that this current is up-regulated in pathological scenarios such as hypoxia (David Saint, Adelaide), ischemia (Peter Light, Edmonton) and heart failure (Albertas Undrovinas, Detroit) and that the distribution is altered across the wall of the heart (Charles Antzelevitch, Utica), while others showed that the current could be switched on by mutations in the C-terminus of the $Na_v1.5$ α-subunit (Robert Kass, New York). There was also consideration of the cellular mechanisms, such as AMP kinase-an enzyme activated during ischemia, that might activate the late I_{Na} (Peter Light, Edmonton). The possible impact of

such activation was discussed by Alexander Clanachan (Edmonton) who studied Ca^{2+} regulation in the whole heart. A number of other talks covered key aspects related to the regulation of the fast I_{Na}. Lars Maier (Goettingen) described the involvement of Cam Kinase isoforms, where as Erwin Shabata (Iowa) covered the role of caveolae (omega-shaped surface membrane invaginations) in regulating I_{Na}, possibly through $G\alpha_s$.

Although I_{Na} is a key contributor, the regulation of Na^+ and Ca^{2+} by no means stops with the I_{Na}, as there are numerous other mechanisms that also transport Na^+ and these can also be up- or down-regulated in pathophysiological states: Godfrey Smith (Glasgow), for example, showed how the Na^+:Ca^{2+} exchanger is up-regulated in myocardial infarction, although the consequences of such remodelling are not always easy to demonstrate. Such Na^+ transport mechanisms, linked to Ca^{2+} homeostasis are critically important because changes in Na^+ will result in changes in Ca^{2+} and thus contractility. The situation is even more complex when regions of the heart become ischemic, and pH_i decreases so that the cell needs to extrude acid. Richard Vaughan-Jones (Oxford) explained how Na^+/H^+ exchange and Na^+/HCO^{3-} co-transporter are involved in regulating myocardial acid-base balance. After a further series of talks on the regulation of Na^+,K^+-ATPase, (Donald Hilgemann, Dallas), ATP metabolism (Joanne Ingwell, Boston), mitochondrial Ca^{2+} (Brian O'rourke, Baltimore), cell-cell coupling (Kenneth Spitzer, Utah), autonomic influences (David Paterson, Oxford) and the clinical relevance of inherited Na^+ channelopathies (Hanno Tan, Amsterdam), the summing up by Wayne Giles (San Diego), William Barry (Salt Lake City) and Dan Roden (Nashville) focussed on the implications of an activated late I_{Na} with respect to arrhythmias, particularly in ischemia and other types of heart disease.

Munir Hussain
University of Liverpool, UK

Lessons from a Physiological Society Meeting

Frank Mojiminiyi (pictured below) relates his experiences as a foreign guest at the King's Meeting

I was privileged to attend the December 2004 meeting of the Physiological Society held at King's College, London as a foreign guest invited by Lucilla Poston. Without the Society's sponsorship, it would have been impossible to attend the meeting, and I am grateful for this opportunity. The meeting left lasting impressions on me with ripple effects on my colleagues and students. I hope that this scheme will be continued so that physiologists from poorer parts of the world can attend Society meetings and be the better for it.

On Friday, 17 December I headed, with excitement, to New Hunt's House to listen to 'tales from the crypt'. The British weather was at its best: so there was a drizzle which became increasingly heavier! Unfortunately, I took a wrong turn, arriving one hour later, and drenched. As I entered, a coffee break was in progress. As I took one faltering step after the other towards the delegates, a bespectacled man in a cardigan walked briskly towards me. He gave a welcoming smile and led me to the table laden with refreshment. His gesture was so reassuring! However, before I could breathe a word of thanks, he had disappeared into the crowd. I knew from the programme that the 'tales from the crypt' symposium was in honour of Richard Naftalin. So, naturally, I looked forward to seeing him. As the symposium progressed, however, I realized that I had already met him – he was the one that welcomed me! I had learnt my first lesson: assuming I ever do well enough to have a symposium organized in my honour, I should be humble enough to wait on those who attend. I should also try to be xenophilic!

'Tales from the crypt' were very interesting. Papers presented were eclectic. But the papers that I remembered most were those that presented novel therapeutic approaches to malaria and diarrhea – two diseases decimating children in the Third World, including Nigeria.

During my visit, I had the privilege of listening to world class scientists. To me the most memorable was Gerhard Giebisch's lecture. His delivery was masterful and classical. And that, at such an age! I was happy to meet in flesh somebody I had read about so much in the renal physiology literature.

I was impressed by the number of Chileans, scientists and students, at the Meeting and hope that one day soon the Physiological Society will organize a joint meeting with the Physiological Society of Nigeria. Maybe we'll hire David Yudilevich to wave the magic wand for us!

A lifeline from the University of Nottingham

As I walked round the posters in my Nigerian outfit on the last day of the King's Meeting, I met a middle-aged man at his poster. After exchanging pleasantries, he asked out of the blue 'Would you mind having some equipment we are no longer using in our department at Nottingham?' I wanted to ask him if he was a mind reader but thought this might be considered rude. Amazingly, just before I arrived at his stand the thoughts on my mind were centred on who I could approach for help with equipment donation. Of course, I answered in the affirmative, I later listened to his beautiful work on integrative physiology. The amiable man I'm talking about is Terence Bennett of the University of Nottingham. As I write these lines, arrangements are in top gear to send us old but functional equipment from the University of Nottingham. To me my trip has been a success – but we need help with the shipping! I would me glad if anybody reading this may know any organization that could be of help.

Lessons and gratitude

The lessons I learnt during my visit as a foreign guest could be summed up in one word: **altruism**. The mission statement of the Physiological Society is quintessentially altruistic, as is my sponsorship as a foreign guest and equipment donation by the University of Nottingham. So how do I show my gratitude or that of the Physiological Society of Nigeria? We will respond by chorusing *E seun! Ime la oh! Mun gode!* (Thank you!). May the tribe of the members of the Physiological Society increase!

PS Donations of old but robust and functional equipment may be welcome by other departments of Physiology in Nigeria. If you would want to help please contact the author at mojiminiyi@yahoo.co.uk

Acknowledgements

I am very grateful to Lucilla Poston for nominating me for the foreign guest scheme and for her support over the years. Many thanks also to David Eisner, Jeremy Ward and Terence Bennett, and to Helen Close for making my trip painless!

Frank Mojiminiyi
Usman Dan Fodio University, Sokoto, Nigeria

In our next issue, Frank Mojiminiyi's *Letter from … Nigeria* looks at the development of physiology in his own country.

Two weeks in the life of...

Lesley Anson, *Physiology News* Editorial Group member, shares two particularly exciting weeks in her other life as a *Nature* editor

Lesley Anson (above); *Nature*'s offices on Crinan Street (below); *Nature* (opposite)

Friday

I wake-up slightly disorientated and in unfamiliar surroundings. My body has no idea what time it is, though the clock next to me tells me that its 7 a.m. I'm in a hotel room near to LAX airport, and its my first trip to Los Angeles, so I start the day full of anticipation.

I jump into my hire car and drive to the California Institute of Technology for a day of lab visits. My first stop is David Anderson's laboratory, where I talk to the postdocs about their work on the innate avoidance to CO_2 in *Drosophila*. After a very pleasant lunch in the Institute's dining rooms, where I am amazed to find Stephen Hawking at an adjacent table, I spend an hour with members of the Caltech Postdocs Association talking about the process of publishing a paper in *Nature*. The rest of the afternoon is spent discussing the structure and function of ion channels with Doug Rees and Dennis Dougherty.

I steal 20 minutes back at the car to jot down as much as I can remember of the day's conversations before I drive to South Pasadena for an entertaining dinner with Henry Lester. I'm interested to hear all about his work on the role of α4-nicotinic acetylcholine receptors in nicotine addiction.

Saturday

After a relaxing morning, I check out of my soulless airport hotel to drive to a more interesting affair in Long Beach. It's a low-budget motel, but right on the beach, so perfect for those early morning runs that I'm planning. I'm in Long Beach for the Biophysical Society meeting. There are many reasons for editors to attend scientific meetings but, most importantly, it enables us to keep abreast of current trends in the field, to hear about new and exciting work and to engage with scientists (often over a dinner table). I walk the mile or so to the conference centre to register for the meeting and find my bearings. In the evening I join David Julius for sushi and an extremely interesting conversation about the strengths and weaknesses of some recent *Nature* papers.

Sunday

Sunday morning lethargy puts paid to the idea of running, but I make it to an excellent symposium on TRP channels, where I bump into an ex-colleague who is now working in industry. After securing an invitation to visit her lab later in the year, I spend the afternoon wandering round the many posters on display.

My evening begins with a brief tour of the 1930s Art Deco interior of the RMS Queen Mary, followed by a lively dinner with Colin Nichols debating the relative merits of single channel versus macroscopic ion-channel currents.

Monday

I studiously ignore my running shoes when I wake up and head straight over to the conference centre for an excellent platform session on inward rectifier potassium channels. The day unfolds in an interesting way. I have two quite frank conversations with different authors about the reviewers on their respective manuscripts. In one case, we talk about what we think they may say. In the other case, we discuss what they *actually* said. Neither conversation was easy, but they were ultimately quite helpful discussions.

In the evening I join 5,000 other biophysicists at the Society reception and dance, followed by a general move across the road to an Irish bar.

Tuesday

This morning, I make the fatal mistake of checking my e-mail account. While I'm out of the office, I leave my files in the very capable hands of my colleagues, but my curiosity nearly always gets the better of me and this morning is no exception. Consequently, I don't make it to the conference centre until late morning.

I have a very productive afternoon at the poster session. There are a number of interesting presentations, some of which I hope will end up on the pages of *Nature*. One, I'm sad to hear, has already been submitted to another journal. But I ask the author if he would be willing to give me advance warning of its publication in the hope we might solicit a *News and Views* article.

My last night in Long Beach is full of old acquaintances. I begin by having dinner with my PhD supervisor, Jonathan Ashmore, and then move on to meet a fellow PhD student who has successfully pursued an academic career. We both remark that each other's jobs must be incredibly rewarding, but finish by agreeing that we've each chosen the right path. As tomorrow is my last opportunity to do some science before I fly back home, I decide to remove any temptation to run by packing my running shoes away.

Wednesday…Thursday
I spend the morning trying to catch talks on something I'm fascinated with right now – the mechanistic similarities between ion channels and transporters. Unfortunately, the two sessions I've identified are running in parallel, but I manage to hear the talks I was hoping to.

After some brief goodbyes, I head back to LAX for a relatively comfortable flight back to London due to the spare seat next to me. I arrive home at 2 p.m. the next day, utterly exhausted, but with just enough energy to perform triage on my e-mail account.

Friday
I'm working from home today, and spend most of my time catching up with urgent manuscript matters. In consultation with a colleague, I decide to send two very exciting papers out for review, and receive positive replies from all three referees that I contact within the hour – this is always a good sign.

I also examine a manuscript that has been revised, after review, to assess the extent to which the authors have addressed our reviewers' concerns. In this case, the authors have responded to each and every point and have included additional data where appropriate. I simply send the revision back to our original reviewers for further advice.

Monday
8.05 a.m. I pick up my daily cappuccino from the AMT coffee stand at King's Cross and head to our office on Crinan Street. I'm a creature of habit so, despite my early start, I feel a sense of comfort being back in my regular routine.

After a morning of printing, filing and general administration, I have a quick lunch in the canteen with my colleagues, catching-up with the latest office politics.

At 2.30 p.m. we have our weekly team meeting at which we discuss new submissions and, in particular, those papers that are being sent out for formal peer review. This is my opportunity to explain to colleagues,

from a wide variety of disciplines, why the papers I'm handling are so interesting and important.

4.45 p.m. sees me dashing out of the office in a cloud of dust – just in time to pick up my daughter from nursery.

Tuesday
I arrive at the office today clutching a pair of manuscripts that I've read since leaving the office yesterday afternoon and I begin to action them appropriately. Sadly, we receive many more manuscripts than we are able to publish – approximately 95% are ultimately rejected – so most papers are rejected before they even reach peer review.

The rest of the day is spent in various meetings, including a Physiological Society magazine meeting at the Society's London office. And as soon as I return to Crinan Street, I am whisked into our weekly *News and Views* meeting, in which each editor talks excitedly about important or newsworthy papers they have accepted in the last week. I sit back and enjoy all the presentations.

Wednesday
Today, my husband and I reverse roles, so 8 a.m. finds me dropping our daughter off at nursery. I make it to work by 9 a.m. which leaves me 30 minutes to comment on a colleague's paper before the noise levels in our open-plan office rise to their 9.30 a.m. high.

My next task is to send a letter that I have only dreamt of receiving – I formally accept a manuscript for publication in *Nature*. Minutes later, an advance copy of tomorrow's issue (pictured) lands on my desk containing two Letters to *Nature* that I handled. Even after six years of manuscript handling, I still get a thrill from seeing the areas that I handle published in the journal.

I leave the office at 4 p.m. to attend a seminar at UCL by Chris Miller, who gives a characteristically clear, interesting and animated presentation about the unexpected transporter activity of a prokaryotic chloride 'channel'. The seminar (or maybe the wine afterwards) somehow triggers a lively debate about the reductionist approach of biophysicists, versus the more contextual approach of molecular neurobiologists, which lasts well into the evening. As an editor, of course, I was able to speak for both sides.

Thursday
Today I'm looking forward to a relatively normal day in the office. I spend the morning doing general manuscript administration – fielding e-mails from authors, seeking advice from referees and drafting decision letters to authors.

After a 4 mile run along Regent's Canal with my colleagues at lunchtime, I turn my attention to a couple of files that have a full complement of reviewers' reports. One is very straightforward – the reviewers agree its an important story, but suggest a couple more experiments to make it watertight. This will undoubtedly make it through to publication. The other is more complicated because there is disagreement amongst the reviewers. However, a quick chat with the most negative reviewer persuades me that it's a case worth pursuing, at least for the time being.

At 4.45 p.m. I fill my bag with manuscripts in anticipation of a peaceful day of reading at home tomorrow. Thankfully, not every day in the life of a *Nature* editor is as exhilarating as the last two weeks have been.

Ten papers on motor control that have been tough acts to follow

Peter Ellaway continues our series with a personal list of papers that have caused him to think most about the elements of motor control

Peter Ellaway

What an invidious task, to pick out your 10 best papers of all time. My first inclination was to go for classics, and there is certainly something of that theme in my choice. So here, at the risk of surprise, umbrage, indifference or other emotions amongst fellow physiologists, are my personal choices. It is a collection of papers that, over the years have caused me to think about the elements of motor control more than most.

Overall, there are three mini themes in the collection. The first is the functional organisation of the corticospinal drive to muscles in primates, including man. The second overlaps with that theme and concerns the order of recruitment of motor units and development of muscle tension. The third theme is the most personal selection as it is the field that has fascinated me for 40 years, since I had the good fortune to be introduced to it by Jim Pascoe, namely the muscle spindle and its efferent control.

1 Functional organisation of the primate motor cortex

Amongst the galaxy of names that helped make the move from phrenology to physiology of the brain, and the motor cortex in particular, David Ferrier stands out. In this paper, Ferrier took up the electrophysiological approach pioneered by Fritsch and Hitzig on dogs and used faradic stimulation from an induction coil to map the motor cortex of primates in terms of movements. Although a large number of contemporary and later investigators joined in the task of identifying specific motor areas of the cerebral cortex, these early observations by Ferrier represent a major move from purely anatomical to functional localisation. Ferrier, of course, went on to explore much more of the brain and this is recognised by the accolade from Sherrington (1906) who dedicated the 'Integrative action of the nervous system' to him.

Ferrier D (1875). Experiments on the brains of monkeys. Proc Roy Soc Lond 23, 409-430

2 Corticospinal actions on individual muscles

This article by Phillips and Porter on the pyramidal projections to the baboon forearm stands out as a comprehensive collection of neurophysiological investigations of the motor apparatus most likely to closely resemble the human arm and hand. Among the features of pyramidal tract function relating significantly to dexterity of primate hand function is the evidence that motoneurones of distal muscles receive a far more extensive innervation than motoneurones to more proximal muscles. Monosynaptic excitatory post-synaptic potentials (EPSPs) in motoneurones of intrinsic hand muscles were invariably seen in response to cortical stimulation whereas around 50% of large motoneurones of proximal muscles lacked EPSPs, emphasising the tight coupling between cortex and motoneurones of hand muscles. Moreover, inhibitory post-synaptic potentials were often elicited in motoneurones of proximal muscles. Despite the passing of another 40 years, today's textbook accounts mostly fail to mention these mechanisms and concepts that Phillips and Porter were instrumental in establishing.

Phillips CG & Porter R (1964). The pyramidal projection to motoneurones of some muscle groups of the baboon's forearm. Prog Brain res 12, 222-245

3 Corticospinal action revealed by spike-triggered averaging of EMG signals

Understanding of how motoneuronal activity is controlled benefited from the introduction of spike-triggered averaging (STA) by (Mendell & Henneman (1971). *J Neurophysiol* **34**). Fetz & Cheney used STA to advance our understanding of coordinated actions of the primate forelimb muscles. Previous studies, using stimulation of the motor cortex and lesion experiments, did not reveal the divergence of individual corticospinal neurones to motoneurones of different muscles. Also, experiments in anaesthetised animals naturally could not reveal normal connections. Using awake monkeys Fetz and Cheney examined the relation between the discharges of individual motor cortex cells and the activity of specific wrist and finger muscles during voluntary task-related activities. Post-spike facilitations (PSF) of motoneuronal activity were triggered from precentral cortical cells whose activity covaried with wrist movements. Paired discharges of single cortical cells were associated with particularly prominent PSF of motoneuronal activity, an action predicted by the work of Phillips and Porter. The characteristic amplitude and time course of the PSFs allowed them to conclude that the cortico-motoneuronal connections were monosynaptic and, importantly, that the corticospinal neurones frequently supplied divergent connections to more than one muscle.

Fetz EE & Cheny PD (1980). Post-spike facilitation of forelimb muscle activity by primate corticomotoneuronal cells. *J Neurophysiol* 44, 751-772

4 Transcranial magnetic stimulation of human motor cortex

High voltages are needed to penetrate the human skull to stimulate the motor cortex (Merton & Morton (1980). *Nature* **285**) and this is really quite painful. It was therefore of considerable interest to neurophysiologists when Merton (1985) placed the magnetic coil (developed as a peripheral nerve stimulator by Barker and colleagues) over his own head and observed a muscle twitch without discomfort (*J Physiol* **369**). This paper by Day *et al*. constitutes a thorough comparison of the effects of electrical and magnetic stimulation. Significantly, the precise timing of discharges of single motor

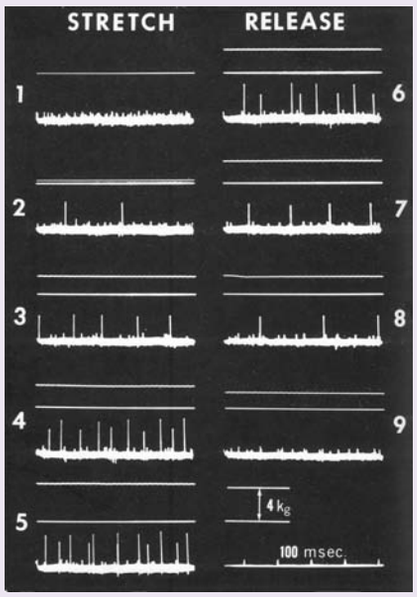


Figure 1. (Figure 1 from Henneman E *et al.* 1965).The responses of one small and one large motoneurone in response to stretch of the triceps surae muscle. Stretch increases from panel 1 to panel 5 and decreases from panel 6 to panel 9. The amount of tension developed by stretch and reflex contraction is signalled by the gap between the two horizontal lines on each trace. Note that the smaller unit is recruited first and de-recruited last (reproduced with permission).

units could be related to the classical D (direct) and I (indirect) wave components of the corticospinal volley observed by Patton and Amassian in the 1950s. I waves result from stimulating intracortical afferents or neurones, whereas D waves result from direct stimulation of the output axons of pyramidal tract neurones. Day *et al*. found early histogram peaks with anodal electrical stimulation but not with magnetic stimulation and argued that magnetic stimulation was indirect. This set the stage for transcranial magnetic stimulation to be used as a tool for assessing motor cortical excitability.

There is one thing that detracts from this paper – the authors thought they were holding the coil the other way up! An erratum (*J Physiol* 1990, **430**, 617) corrects the mistake. Fortunately, only the authors' pride and not their inferences were affected.

Day BL, Dressler D, Maertens de Noordhout A, Marsden CD, Nakashima K, Rothwell JC & Thompson PD (1989). Electric and magnetic stimulation of human motor cortex: surface EMG and single motor unit responses *J Physiol* **412**, 449-473

5 Orderly recruitment of motor units and the size principle

A second theme addresses the motor unit, and how intrinsic properties as much as synaptic inputs form the basis of how motor acts are controlled. With the advent of single unit EMG recordings and working in Sherrington's laboratory, Denny-Brown began to formulate the basis of a size-dependent, orderly recruitment of motoneurones. He observed that voluntary and reflex movements always began with the discharge of the same motor units, and those tended to be the small units. However, it was Henneman's research on decerebrated cats that firmly established the key evidence and arguments for the size principle. Henneman was able to make his conclusions by recording from fine ventral root filaments containing only a few motor axons (Fig. 1). Under those conditions, the size of motoneurones could be judged by the amplitude of their action potentials. His work strongly indicated that the intrinsic biophysical properties of motoneurones might account for orderly recruitment. Consideration of muscle activities ranging from manipulative hand movements to the athletic achievement of long distance running, and the understanding of fatigue and movement disorders, all owe their advance to the size principle and orderly recruitment pattern established by Henneman.

Henneman E, Somjen G & Carpenter DO (1965). Functional significance of cell size in spinal motoneurones. *J Neurophysiol.* **28**, 560-580.

6 Functional specialisation of motor units

Burke employed intracellular stimulation of motoneurones to ensure isolation of single motor units in his studies. Twitch contraction time, tetanic force and fatiguability allowed separation of motor units into three types. Two types had rather short twitch contractions but could be distinguished as either fatiguable (FF) or fatigue resistant (FR). A third type (S) had a relatively long contraction time, developed substantially less tetanic force, but was very resistant to fatigue. Glycogen depletion established three histochemical profiles matched to the physiological properties. Figure 2 from the paper graphically emphasises the separation of motor unit properties and does away with need for a statistical affirmation of the FF, FR and S classification! The paper anticipates that the distinctive attributes of motor units might be tailored to the functional demand made on particular muscles. It has provided bedrock for later and on-going studies of how muscles of different unit composition are suited to their tasks, and the degree to which those properties are plastic and can change when duty cycles are

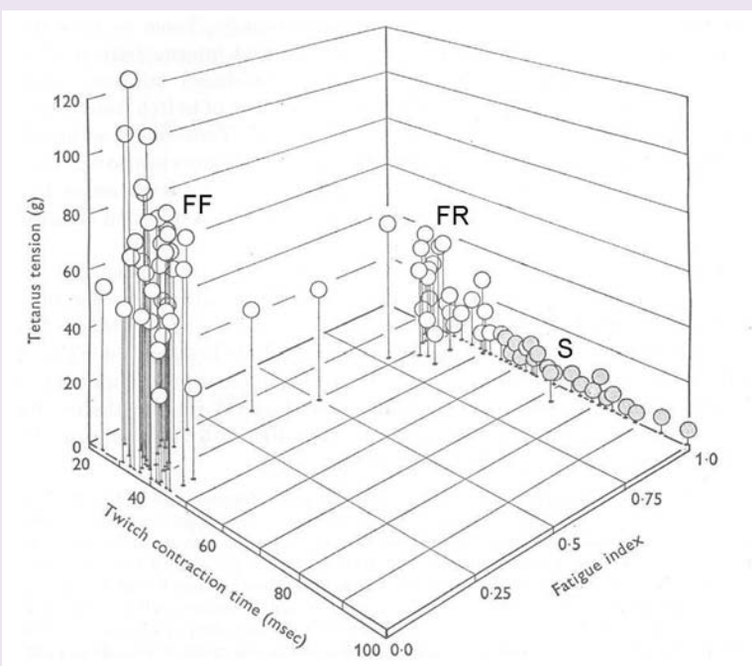


Figure 2. (adapted from Figure 5 from Burke *et al*. 1973) The plot relates tetanic force to twitch contraction time and fatiguability of individual motor units of the cat gastrocnemius muscle. A fatigue index of one denotes no "sag" in the force developed by repeated titanic contractions whereas zero indicates inability to sustain force output.

deliberately manipulated, as in athletic training and physiotherapy.

Burke RE, Levine DN, Tsairis P & Zajac FE (1973). Physiological types and histochemical profiles in motor units of the cat gastrocnemius. *J Physiol.* **234**, 723-748

7 Dependence of muscle tension on desynchronised firing of motor units

Citations for this paper are high (550 since 1980) probably because of an elegantly simple experiment. Ventral roots containing all motor axons to the soleus muscle were sub-divided and then recombined until five groups of rootlets were obtained that when stimulated each produced roughly the same muscle twitch. When all five bundles were stimulated synchronously at 5 impulses/sec a grossly unfused train of twitches was elicited. In contrast, in response to distributed stimulation of each bundle of ventral rootlets in turn, but at the same rate, a practically fused contraction was obtained immediately *and* the force generated rose above that achieved with synchronous stimulation. Thus, Rack and Westbury showed that asynchronous, repetitive activation of motor units develops force more usefully than synchronous stimulation. This is likely due to the mechanical interaction between the widely overlapping muscle fibres of individual motor units. Latterly, cross correlation of the discharges of single motor units has shown very little evidence of synchronous firing during voluntary muscle actions. The neural mechanisms working to minimise synchronous discharges of motoneurones are clearly matched by the distributed nature of muscle fibre territory of motor units to produce smooth contractions with economy of effort.

Rack PMH & Westbury DR (1969). The effects of length and stimulus rate on tension in the isometric cat soleus muscle. *J Physiol* **204**, 443-460

8 The follow-up servo theory

These final three papers indulge my interest in the muscle spindle. This review draws together the key evidence in support of the follow-up servo theory. Merton's original experimental evidence from studying the silent period caused by an electrically induced twitch during a voluntary contraction is there, as are the experiments with his co-authors Hammond and Sutton on the stretch reflex. This was a very seductive theory in that it provided a role for the gamma motoneurone innervation of muscle spindles, namely to provide a command signal to the spindles as part of a follow-up servo control of muscle length. As with all good theories it spawned a huge amount of experimental work that, while contributing to its own demise, greatly advanced our understanding of the role of these complex receptors. The follow-up servo theory requires muscle spindles to fire in advance of contraction. Telling evidence against the theory came with the advent of the microneurographic recordings showing that voluntary contraction starts just ahead of an increase in spindle discharge (Vallbo (1970). *Acta Physiol Scand* **78**, 315-333). Nevertheless, far from discrediting the experimental data obtained by Merton and colleagues, it simply shifted the emphasis of the theory to that of servo assistance dependent on co-activated discharges of alpha and gamma motoneurones.

Hammond PH, Merton PA & Sutton GG (1956). Nervous gradation of muscular contraction Br Med Bull 12, 214-218

9 Static and dynamic gamma motoneurones

Prior to the 1960s it was thought that gamma efferent axons simply biased the discharge of spindle afferents. This paper firmly establishes the separate identity of two types of gamma motoneurone, one controlling the static and another the dynamic nature of primary spindle ending discharge to stretch of the muscle. Jansen and Matthews (1962. *J Physiol* **161**, 357-378) had previously suggested that such a dual system might exist, based on their observations of the dynamic response of primary endings to central stimuli. Also, around this time there had begun the hugely enjoyable dogfights at Physiological Society meetings between Barker and Boyd that eventually established two histologically different intrafusal muscle fibres (bag and chain) and related motor endings (plate and trail). Of particular importance in Crowe and Matthews' paper was the finding that any one gamma motoneurone invariably had the same action (static or dynamic) on all the spindles that it innervated, and that static fusimotor drive was capable of sustaining spindle afferent firing during release of a muscle from stretch. The implications of these findings for the role of spindles in complex movements that involve extensive lengthening and shortening contractions of limb muscles (such as locomotion) have been considerable.

Crowe A & Matthews PBC. (1964) Further effects of static and dynamic fusimotor fibres. *J Physiol.* **174**, 132-151

10 The single static gamma efferent linked to intrafusal muscle trail endings

I had the good fortune to be in Laporte's laboratory at the time of this work and was won over by the audacity of the experiment. At the time there was an urgent need to establish the relation between static and dynamic gamma motoneurones and the two types of intrafusal motor endings, trail and plate. The experiment Laporte devised was to isolate a small, functionally intact ventral rootlet that contained only one efferent axon to a muscle. When such a rootlet was found to contain a gamma efferent, the remaining ventral root supply to the limb was cut and the innervation allowed to degenerate over a period of days. In a second stage, the discharge of spindles was recorded in response to sinusoidal stretch of the muscle, with and without stimulation of the surviving gamma efferent. An increase in overall frequency of afferent discharge, accompanied by a reduction in peak-to-peak fluctuation, identified the gamma efferent as static in all ten experiments. The muscles were then sent from Toulouse to Barker's lab in Durham for silver impregnation. All six of the successful preparations showed only trail type endings. This was a remarkable piece of work considering the skilful combination of surgery, electrophysiology and histology required to achieve a result.

Barker D, Emonet-Dénand E, Laporte Y, Proske U & Stacey MJ (1966). Morphological identification and intrafusal distribution of the endings of static fusimotor axons in the cat *J Physiol* **230**, 405- 428

Peter Ellaway
Department of Movement and Balance, Imperial College School of Medicine, London, UK

Letter from ... Australia

In the first of a new series of letters from overseas Members, David Allen considers grantsmanship

When scientists sit down at a bar, they usually start by talking about the difficulty of obtaining grants in their corner of the world. So I thought I should start with a survey of grantsmanship in Australia and gradually extend to other aspects of science, physiology and university life.

A pivotal event in science funding here was the Wills Report, published in 1998, which advocated a doubling of funds for medical research and preached a 'Virtuous Cycle' in which research, industry and government activities were 'mutually reinforcing'. The Government accepted the plan and research resources have substantially increased, so I should be able to report that it is twice as easy to get a grant as before. But, of course, it is not as simple as that. As part of the package, the Wills Report also suggested a raft of reforms. The net effect of these has been generally positive and has encouraged commercial and clinically-orientated research and increased the competitiveness and mobility of government-funded research institutes and fellows. In the area of grants, the Wills Report wanted more priority-driven research performed by larger, collaborative groups who could carry research from basic science through to clinical practice.

The National Health and Medical Research Council (NH&MRC), who manage medical research in Australia, were placed under tremendous pressure to revamp the funding mechanisms to reflect the Wills Report. The bulk of the additional funding has therefore been directed to 'New Programme' grants in which typically 3-6 successful scientists agree to collaborate over 5 years to work on a broad area of perceived medical importance. These new programmes have prestige, longer term funding and are often financially more rewarding, so scientists across the country have been networking furiously to squeeze themselves into the constraints of the new model.

Unlike in London, David Allen never puts on his Wellington boots when he strays into his garden

Does it work? Does the new funding model lead to the desirable objectives the Wills Report advocated? The NH&MRC is required to report to the Government on the success of the changes, and the additional funding will potentially be withdrawn if improved health and medical outcomes cannot be demonstrated. Needless to say, the NH&MRC will do its best to convince Government! But the sad truth is that in the organization of funding for medical research, it is political fashions that rule the day, and evidence-based assessments, now the touchstone of medical activities, are hardly involved.

Surprisingly, support for medical research in Australia has arisen from an unlikely source. Access Economics, an independent economic analysis group, was commissioned to determine the value of investing in Health Research & Development. They placed a dollar value on the 8 year gain of life expectancy experienced between 1960 and 2000 and made the critical assumption that half of this improvement could be attributed to global health R & D. With a few more assumptions it turns out that a $1 spent on Health R & D generates $5 in improved health returns *each year*. This stunning outcome ought to impress even the most economically orthodox government.

Clearly medical research has received generous treatment from Government sources, but Australian universities have not received the same largesse. By chance the current Minister for Education, Brendan Nelson, visited our department some years ago when he was a lowly MP. When we tried to press on him the value of a buoyant university system and the difficulty of maintaining education standards when funding per student fell each year, he replied that his constituents never complained to him about universities. However, he has proven an effective Minister whose philosophy is that all universities do not need to be the same (code for 'research funding can be withdrawn from some') and that the additional funding he now agrees the

The old medical school at the University of Sydney which houses the Departments of Anatomy and Physiology (*photo by Marie Ward*)

universities need will come from increased student fees. Not exactly a surprise given world-wide trends, but at least Australia has a relatively generous form of student loans. These loans need not be repaid until income exceeds a threshold close to the national average and are interest-free after correction for inflation.

My main concerns about the developments in medical research in Australia revolves around the institute vs university competition. Both systems have advantages and disadvantages, but the growth of medical research here appears currently to be mainly in the institutes. I have a very attractive laboratory in a century-old sandstone copy of an Oxbridge college; nevertheless, when I visit my colleagues in a successful institute the difference can be striking. They have new laboratories in magnificent, purpose-designed buildings with more buildings planned, and are actively looking for new staff at all levels. The restricted funding of universities means that we have difficulty competing except for the availability of students. Of course, the superior position of institutes reflects the fact that they go out into the community, and particularly to politicians, and actively raise funds. No one wants to deny them the success that this effort brings, but university departments and researchers find it very difficult to compete given the public and political perceptions of universities.

I came to Australia from the UK in 1989 and frequently have to field the question 'why did you leave ?'. Australians thought that the answer was 'lifestyle' though initially I was uncertain quite what they meant. It turns out that Australians have an unshakeable belief in the quality of their lifestyle and, whether or not it is true, it is mildly infectious. I can report that the sun shines almost every day and, unlike in London, I never put on my Wellington boots when I stray into my garden. English colleagues were genuinely concerned that I was moving to an arid and isolated academic climate.

Left: Sydney Harbour and bridge
Below: Lake McKenzie. David Allen (left), NZ physiologist Marie Ward (right) and assorted partners walking the Routeburn Track in New Zealand

(*photos by Marie Ward*)

However, times have changed and I now more frequently receive polite questions about the career opportunities in Australia. The Australian government has seen the value of asset-stripping scientific expertise and has extremely generous Federation Fellowships to fund successful scientists who choose to relocate here. Trevor Lamb and Martin Johnson are two UK physiologists who have received such fellowships, although the latter had a change of heart at some point and decided to stay in Cambridge. And the laboratory next to mine is empty right now...

Finally, to end with a suggestion that might enhance trans-global links, what about a joint Australian/UK Physiological Society meeting? Or, even better, how about two, one in Australia and the other in the UK. The Australian Physiological Society is enthusiastic and fares are cheap in cattle-class. In a non-IUPS year, I suspect the numbers prepared to make the journey would be substantial and cross fertilization would undoubtedly occur.

David Allen
Department of Physiology,, University of Sydney, Australia

David Beech, pictured here, left, with Dirk van Helden, was the Society's visiting Australasian Lecturer during 2004. As part of his programme David gave the Australian Health and Medical Research Congress (AHMRC) plenary lecture, visited the University of New South Wales and presented seminars at the Department of Pharmacology, Melbourne University and at the Departments of Physiology at Monash University and the University of Queensland. A review covering the subject of the AMHRC lecture has been accepted for publication in *Clinical and Experimental Pharmacology and Physiology.*

Anatomy for Beginners

***Physiology News* Editorial Group member John Lee recently co-presented Channel 4's series. Here he discusses the programme with Austin Elliott**

Austin Elliott (AE) A couple of years ago you appeared in Gunther Von Hagens' televised public autopsy. How did you first meet him and get involved with that?

John Lee (JL) I went along to see his Bodyworlds exhibition, which I thought was excellent. I was particularly interested by the reactions of the other people visiting – children and adults of all ages – who were enthralled at the opportunity to find out something more about their own bodies. I arranged to meet Von Hagens and discuss the exhibition with him, and during this conversation, he mentioned that he was thinking of carrying out a public autopsy and asked my opinion on it. I said that it could be a valuable thing to do, but was unlikely to be permitted. When Von Hagens went ahead with the public autopsy, he contacted me and invited me to participate. Initially I declined, for a whole variety of reasons, mainly political rather than educational. But in the end I decided that the benefits would probably be worthwhile, so decided to take part.

AE When did the idea for *Anatomy for Beginners* come up?

JL Following the autopsy both Channel 4 and Von Hagens were keen to do something further involving showing the public anatomy, and various discussions were held over the next year or so. Although some of these involved me, at that stage I thought that someone else would probably be better placed to help with the series. However, political pressures and personal choices meant that none of the people I suggested were in fact able to take part. A different production company subsequently got involved and the idea came back to me a relatively short time before the series was due to be filmed. Following detailed discussions on the aims of the series and how it would be carried out, I agreed to participate. I was then closely involved in the planning stages, as well as in the actual filming.

John Lee and Gunther Von Hagens prepare for filming

AE Where did the bodies for the series come from?

JL Von Hagens runs an extensive body donation programme, in which people who have seen his exhibition or who wish to donate their bodies for educational purposes, contact him and leave their bodies to the Institute for Plastination in Heidelberg. These formalities are carried out in accordance with German law and involve full consent for educational dissections and post-mortem display of their bodies or body parts. Body donation seems to be quite popular, since Von Hagens has accumulated several hundred bodies over the last few years and has many more people queuing up to donate theirs.

AE Could you have made the series in the UK?

JL I think that this is very doubtful. Even if it were theoretically possible under existing regulations (which is probably not the case), any UK anatomist who attempted such a series would have extreme bureaucratic and political pressure placed on them not to go ahead. It seems to me that the current attitude of the authorities can be summed up as being closer to 'anything for a quiet life', rather than 'is this suggestion worthwhile and would it produce some benefit'.

AE Were the bodies that were used fresh or preserved in formalin?

JL Two of the bodies were fresh. Not fresh in the sense that they had only just died – the deceased individuals had been stored frozen and were then thawed for the dissections. These unfixed bodies were used for the programmes on movement and on circulation and respiration, because carrying out some of the demonstrations that we performed required pliable tissues. The remaining two bodies, those used for the programmes on digestion and reproduction, had been perfused with formalin and were therefore fixed. Fixation makes the body tissues much firmer and was necessary both for preserving the gut and also for allowing dissection of the small and delicate tubules of the male reproductive system in particular.

AE The audience in the series were applauding politely, but some wincing was apparent at times. Did you have to make any cuts because anyone ran for the exits?

JL No, no-one ran for the exits. In fact I felt that the televised audience reaction shots were not really representative of the audience response. Television people like to introduce a bit of drama into the proceedings in the editing, but in fact the audience sat quietly and intently during the 3-4 hours it took to film each programme. Their interest was reflected in the sensible and thoughtful questions they asked in the (mainly non-televised)

question and answer sessions that we ran immediately following the dissections. Many of those in the audience had in fact enrolled in Von Hagens' body donation programme.

AE Was it all live or did you have to do more than one take? Did the cameramen have to have especially strong stomachs?

JL The series was filmed live. We had worked out a running order for each programme – in other words the general order in which we planned to carry out the dissection, use the props and explain what was going on – but apart from Von Hagens' initial introduction, there was no script and no autocue. We occasionally had to repeat a point or show something slightly differently in order for the director to get the right shot, and we sometimes paused the action for technical reasons while the dissection was progressed or while the cameras moved. But basically the feeling of it was that of giving a demonstration lecture to an audience, though with cameras and paraphernalia doing things in the background. I must say that I thought the cameramen, and indeed the entire crew, were exceptionally professional, since this was the first time that most of them had ever seen anatomy. In fact, this gave the production something of a buzz, since most of the crew were as fascinated by the proceedings as the studio audience.

AE In the shows you seemed to be talking mostly about physiology, rather than pathology. Was this intentional?

JL In a general sense, it always seemed to me at medical school that anatomy, physiology and pathology were the three cornerstones of medicine: what it is, how it works and how it goes wrong. In planning the programmes we felt that simply showing anatomy would make little sense to the audience unless we tried to explain something of what it is for. This then inevitably leads into some thoughts about how things go wrong. In trying to figure out what to talk about, I tried to pick things that were simple to explain, but also sufficiently common that many people would have had direct or indirect experience of them.

AE You trained in medicine, then did a PhD in muscle physiology and subsequently specialised in pathology. Do you think pathologists are 'medical physiologists in disguise'? People usually say that anaesthetists are the physiologists within medicine.

JL The specialty of anaesthesia certainly does show what can be achieved by clear-headed applied physiology. As a pathologist, I think of myself as a specialist in disease and disease mechanisms. I certainly think that a good understanding of basic physiology is necessary to be an effective pathologist. It's not so much that pathologists are medical physiologists in disguise, but rather that their job is to study perturbed physiological systems rather than controlled normal functioning.

AE Do you think anatomy/physiology/pathology is best 'brought home' to the public by a live show? Or by something like Von Hagens' Bodyworlds exhibition?

JL I think both are valid methods of education. An exhibition allows people to go round at their own pace and to go into things to their own level of detail. On the other hand, a television series reaches a very wide audience (between 1.5 and 2 million for each of the four programmes) and has an immediacy which is difficult to achieve in any other way. The studio audience validates the experience for the television audience. And, as we all know from attending demonstrations of whatever subject, there is something about seeing the real thing that especially draws and holds the attention.

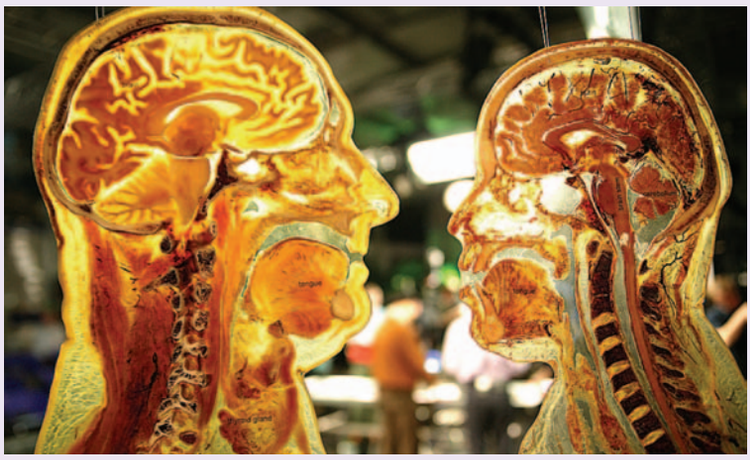
AE A couple of things that stood out for me were pulling the tendons to clench the fist and the inflation of the lungs – physiological bits of anatomy, I guess.

JL Yes, it has been interesting talking to people who saw the programmes. Many people found those parts fascinating, but in fact there has been a wide range of items highlighted by different individuals on the basis of personal experience or interest. Personally, I was interested to see the skin being removed as a whole organ and also to see the oesophagus dissected from behind, among other things. We tried to include items that would interest people with no experience of anatomy, but also some which would not have been seen by even experienced anatomists.

AE You mentioned above that the show could probably not have been done in the UK for legal reasons. There was a lot of objection to the public autopsy and to Von Hagens' Bodyworlds exhibition at the time. Indeed, even the British Medical Association was rather 'anti', judging from some of the commentary on Channels 4's Bodyworlds website. Do you think attitudes are changing? Do you think that regulations governing dissection and anatomy in the UK are too restrictive?

JL I think the response to this series was fascinatingly different from the response to the public autopsy. There was hysterical outcry over the autopsy which was followed by a rather sheepish silence when the sky did not fall and many people found the programme interesting. Remarkably, although *Anatomy for Beginners*

Von Hagens (right) and German artist Joseph Beuys (left) – can you spot the resemblance?



The programmes helped people to think more realistically about their bodies and the way they are constructed.

showed vastly more dissection than the autopsy, it seemed to hardly rate as news. I think that this represents progress of a sort. On the whole, it seems to me that the general public are far more grown-up about the whole subject of anatomy than many of our politicians are. Current UK regulations are extremely bureaucratic and these will be added to by the work of the Human Tissue Authority which is being set up as a result of the recent Human Tissue Act. Although some of the ideas behind this and other legislation related to bio-medicine is perfectly sensible, there does unfortunately seem to be a tendency in the UK to legislate first and not bother to try and think about how it will actually work or affect things until afterwards. I personally do not believe this is good for medicine, science or society as a whole. Incidentally, we also wrote a new website to accompany the series which can be found at: www.channel4.com/science/microsites/A/anatomy/

AE Is this sort of ambiguity of the British towards anatomy new? After all, the Hunter brothers used to do public demonstrations in the 18th century, but after the revelation that Robert Knox's anatomy teaching lectures in Edinburgh in the 1820s had used the bodies of Burke and Hare's murder victims, there was public outcry.

JL That's right, it wasn't a good start. The bureaucracy started then, and ever since the British authorities seem to have had difficulty in reaching well thought out and proportionate responses to issues involving bodies. That this carries on to this day is shown by the institutionalised hysteria in response to, say, the Shipman case, among many other examples.

AE We now have medical schools in the UK with little classical anatomy or dissecting room teaching, and even one medical school with no dissecting room at all. What do you think about this? Did you ever discuss it with Von Hagens, who used to be a medical school anatomy teacher in Heidelberg?

JL Yes, there has been a strong tendency over the last decade or two to remove real practicals and replace them with second class substitutes. There are many reasons for this, though not many of them have much to do with whether this is good for education. Personally, I think that it is extremely worrying that medical students in many medical schools now do little or no anatomy dissection, do not attend autopsy demonstrations and perform few real physiology or biochemistry practicals. It is often stated that students can get this knowledge just as well from books or from computer simulations. I simply don't agree. It seems to me that this attitude is very similar to that which led to the intellectual bankruptcy of medieval scholasticism. In my view, it is very important for students to see and do things for themselves if they are really going to appreciate what practical scientific subjects are about. I think that I would feel cheated as a student if I was aware how little real practical experience I was getting in many science disciplines at modern universities. Von Hagens is obviously passionate about teaching anatomy and I think holds similar views.

AE One science writer I know said she found Von Hagens a bit self-consciously ghoulish, dissecting in his fedora hat and so on … What do you think about this?

JL Yes, many people find it difficult to get beyond the hat and the German accent. People vary in how individualistic they like to be in presenting themselves to a wider audience. Personally, I think that interesting subjects speak for themselves and would rather people concentrate on the subject rather than other paraphernalia, which are really just a distractor.

AE Still on the same topic – to people with knowledge of 20th century art, Von Hagens' personal chosen visual style – hat, sleeveless jacket – is very reminiscent of the German artist Joseph Beuys (recently the subject of a major retrospective at the Tate Modern, 4 Feb-2 May 2005). Do you know if this is deliberate? And why?

JL No idea. I suppose it's possible that this simply represents a local style, in the same way that almost everyone in the UK seems to be wearing black at the moment.

AE Finally, what did you hope that *Anatomy for Beginners* would achieve? Do you think that it realised its aims?

JL I think my hopes for the programmes were simply that they would reach a large audience, interest them in anatomy and help them to think more realistically about their bodies. In particular, that it would allow them to see for themselves important truths about the way we are constructed and to do this in a way which would have a much greater impact than simply seeing a picture in a book. Judging from the audience figures and the overwhelmingly positive response, I feel the programmes did achieve this. If people were left with some arresting images and new ideas that have stayed in their minds as a result of the series, then that is essentially what education is all about.

Public engagement made simple

Erinma Ochu (left), Stuart Allan and Ellen Poliakoff

Getting involved in public engagement needn't cost the earth or take up much time. University of Manchester researchers, Ellen Poliakoff (Psychology) and Stuart Allan (Life Sciences), teamed up with science communicator and filmmaker, Erinma Ochu, to address the issues and present solutions to widening public participation and interest in science whilst facilitating the involvement of scientists with busy schedules. Here Erinma, who also has a PhD in Neuroscience, tells how.

Whilst I enjoy devising new ways to engage scientists and the public, I am acutely aware of the barriers to participating in engagement activities, even though, with much research being publicly funded, there is a professional obligation. Planning activities takes time, especially when scientists work in isolation, planning projects from scratch with no legacy of best practice or resources to guide them. Learning the 'hard way' is time-consuming, exhausting and stressful and will quite possibly put people off getting involved again. Postgraduates are often too scared to ask their supervisors for permission, primarily because of the time commitment.

At Manchester we have devised a series of projects to address these concerns. *A Day in the Life* will show aspects of academic life for plant scientists to physiologists to nanotechnologists, whilst engaging professors to technicians. Scientists will document their everyday lives by taking photographs with disposable cameras and a photographer, David Bennett, has been commissioned to document their days. We want to capture the ordinary as well as the extraordinary lives of scientists: the coffee with colleagues, the lab meetings, jetting off to a conference and the life in the lab, to give the public a better idea of what scientists actually do. We hope to uncover similarities and differences across disciplines and with a touring exhibition and book, we want to stimulate dialogue between scientists and the public about the nature of scientists' work whilst challenging perceptions along the way.

Why science, a documentary film project aims to show why scientists, across all levels, chose to do science in the first place. The premise for the film is to find humorous and personal stories to which the public can relate easily. My career in science began because I couldn't decide whether I should do biology or German at GCSE level. I couldn't do both because the timetables clashed, so I got my classmates to vote and the majority voted biology.

Both projects allow scientists to get on with their daily lives with minimal disruption.

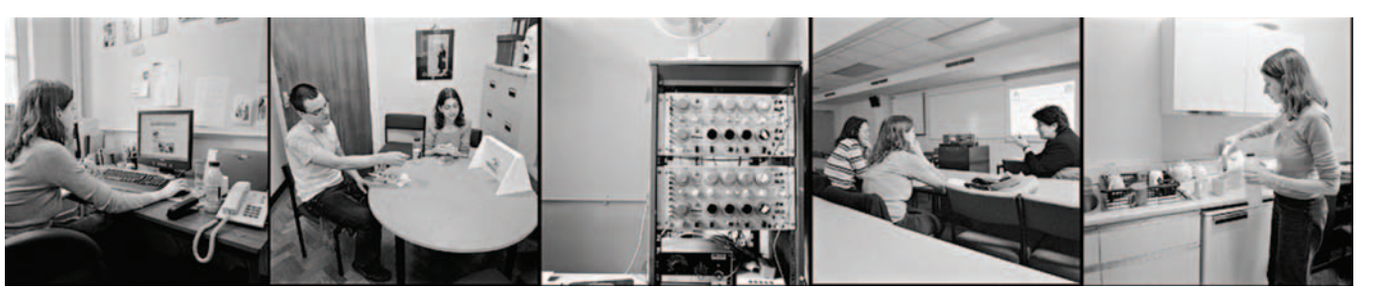
For scientists keen to devise their own engagement activities and with a little more time, we are producing a case study CD-Rom of events that we devised for National Science Week 2005. The CD-Rom will detail how to: register your event at a festival, fund it, find a venue, target your audience, publicise and attract media coverage as well as how to evaluate and monitor it. So, there will be no need to start from scratch. Research Councils (www.rcuk.ac.uk/) also provide funding and opportunities for their scientists to take part in various engagement activities. The Medical Research Council, for example, provides engagement training and the chance to exercise communication skills at public workshops run at Cheltenham and Edinburgh festivals of science.

Another important step is for academic institutions to recognise and reward scientists making the effort to get involved. Thankfully, the British Association for the Advancement of Science is exploring how this might be achieved at their annual science communication conference (www.the-ba.net/the-ba/ScienceCommunication/). We will report back on the conference via www.manchesterscience.blogspot.com, which charts our progress and details other projects addressing engagement issues.

Email us to take part in any projects, particularly *A Day in the life*, but also to find out about planning an event or to simply contribute to the debate: erinma.ochu@manchester.ac.uk

The projects are sponsored by a Wellcome Value In People award, the University of Manchester, a BBSRC, MRC, NERC small grant award and the Medical Research Council.

Erinma Ochu
University of Manchester, UK



Pilot of *A Day in the Life of Ellen Poliakoff*, experimental psychology lecturer (*Black and white photography by Dave Bennett,* http://www.stray-light.co.uk/GalleryD.htm)

Open access

As the debate gathers pace, Liz Ferguson and Bob Campbell from Blackwell Publishing, publisher of the Society's journals, give their views

Open access continues to be a topic for lively debate among authors, societies and publishers. There are three types of open access:

• Pay-to-publish, or 'author pays' publishing

• Self-archiving in institutional, subject or personal repositories

• Free access to articles of a certain type, or after a certain time period, or to certain groups of customers (e.g. developing world), for journals which are usually subscription-based.

Over the past year the debate has gained pace with interest from the UK Government and the US National Institutes of Health (NIH) among many others. After an unusual second round of reports and responses between the UK House of Commons Select Committee on Science and Technology and the Government itself, the Government held its line on pay-to-publish open access not being demonstrably better than the current model, but indicated that the Research Councils might begin to include money in grants for publishing.

The Research Councils have, in fact, just stated that they will allow grantees to request money for publishing and that they will encourage recipients of grants to deposit their work in a repository (with the choice of repository left to the individual). The NIH has produced a clear but controversial policy requesting all recipients of NIH grants to deposit the author's version of the accepted manuscript on PubMedCentral within 12 months of publication. The Wellcome Trust is likely to announce a similar scheme in the near future.

It is clearly attractive to have articles available on an open archive as exposure is widened and there is some evidence from the physics community in particular to suggest that citations might be boosted. Articles published in the *Astrophysical Journal* with self-archiving in the AstroPh server gain approximately twice the citations of articles in the same journal that have not been self archived. There are, however, possible negative consequences that must be considered and these are of particular importance to societies. The table above summarises the main arguments for and against author self-archiving.

PROS	CONS
Author friendly	A fully organised system of Institutional Repositories with improved discovery (Google etc) could enable anyone to access an article without needing to pay, thus undermining the subscription and licensing base
Gives free access to the article	Once subscriptions are lost they are very difficult to win back (it would be a one-way experiment)
Could boost citations (evidence from physics and astrophysics supports this)	Potential confusion if multiple versions of the same article are available. Could undermine the final published version
Would please funding bodies	
Main physics publishers (AIP, IOPP) maintain self-archiving has not damaged their business	The IOPP reports that the downloading of articles archived elsewhere has reduced

We have had many discussions with societies about the implications of both the author pays model and self-archiving; the remainder of this article will focus on the latter.

We carried out a survey towards the end of 2004 into society members' attitudes towards their societies and publications. The results clearly showed that the primary reasons members join societies are for reduced rate conference attendance and for the journals: all members of the Physiological Society, for example, are entitled to free online access to *The Journal of Physiology* and *Experimental Physiology* as a benefit of membership. If many of the articles published in the journals are available free of charge elsewhere on the internet, and can be found relatively easily through new services such as Google Scholar, a large part of the reason for joining the Society will have disappeared. Additionally, librarians are not so easily able to measure usage of the journals and are more likely to cancel: this could seriously undermine the financial stability of many journals and their societies.

Is there really a problem with access to published research? *The Journal of Physiology* and *Experimental Physiology* make their topical reviews available free of charge to all readers immediately on publication, both journals are available in developing countries free of charge or at appropriate rates through various philanthropic schemes, and all the content of both journals is made available free of charge after 1 year.

Taking these factors together with the wide availability to members and to more than 2,000 institutions worldwide, one wonders what the journals stand to gain from initiatives such as the NIH's requesting deposition of the author's version within 12 months. Version control should be considered, particularly if the Wellcome Trust goes through with a plan to create a UK PubMedCentral equivalent that might make a PDF that differs from the published version. One should also ask why, if a journal offers free access after 12 months anyway, there shouldn't

simply be a link to the official version on the journal's own website.

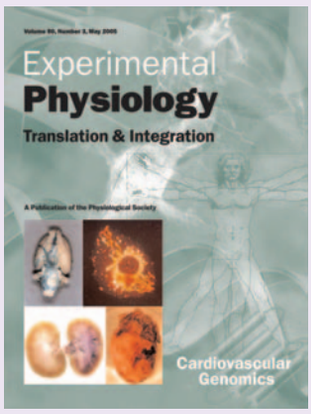
Blackwell and the societies we publish for are in the process of adapting to the changes that some of the funding bodies and the academic community clearly want. We are launching a trial called Online Open with some participating journals (including the journals of the Physiological Society) which will allow authors to pay for their articles to be made available on an open access basis within the journals' sites. We are reviewing usage data with societies to jointly determine embargo periods for individual journals to allow them to comply with requests from bodies such as the NIH while protecting what are, for many societies, their primary sources of income. Once the relevant embargo period is over, authors will be able to post their accepted versions of manuscripts on any repository they choose. From this summer we will allow authors to retain the copyright of their own articles in the journals that we own; some societies, including the Physiological Society, will be doing the same.

The open access debate has developed a great deal over the past 12-24 months. We started this article by introducing the three types of open access; we are responding to all three by experimenting with new models that meet the requests of the research community and its funders. We are doing so in a manner that allows us to always keep in mind the need for learned societies to maintain their income. We look forward to the continued development of scholarly publishing.

Liz Ferguson, Publisher
Bob Campbell, President
Blackwell Publishing, Oxford, UK

Join in the debate

Send us your views on this, or any other aspect of open access, for publication in *Physiology News*.



How exactly does the brain control breathing?

An understanding of exactly how the brain controls breathing is fundamental to the treatment of respiratory disorders. We know that breathing is an automatic rhythmic process that persists without conscious effort whether we are awake or asleep, but the question that has intrigued many scientists for well over 100 years is what maintains this almost fail-safe vital rhythm throughout life?

Experimental Physiology editor Julian Paton (University of Bristol) invited two world renowned scientists – Patrice Guyenet from the University of Charlottesville and Guy Richerson from Yale University – to use the journal as a forum to discuss the issue and attempt to resolve their differences in opinion.

Both authors agree that the respiratory rhythm requires specialised nerve cells (central chemoreceptors) to power the rhythm, but the issue highly debated by Guyenet and Richerson is the precise location and cell types involved. Guyenet proposes that these nerve cells are located in a ventral area of the brainstem (the retrofacial region) and loaded with a transmitter substance called glutamate. Their close proximity to the ventral surface of the brain allows them to sense and react to changes in the pH of the cerebrospinal fluid; this is deemed an essential property of a central chemoreceptor. Richerson, on the other hand, stipulates that central chemoreceptors are found close to the midline blood vessels of the brainstem allowing them to 'taste' the pH of the blood. His cells do not contain glutamate but a substance called serotonin.

Experimental Physiology asked each author to stake out his claim and provide rebuttals and critiques of each others' articles (recently published in *Nature Neuroscience*). The articles (*Exp Physiol* **90**, 247 and 259) are available **free** at http://ep.physoc.org/content/vol90/issue3/

***Experimental Physiology* invites authors with opposing published opinions on topical aspects of physiology to propose *Exchange of Views* topics for future issues. Please contact John Coote at** eward@physoc.org

Biochemical Journal's public access policy

At the 111th Annual Meeting of the full Editorial Board of the Biochemical Journal, it was announced that papers accepted for publication will be deposited automatically in PubMed Central (PMC), the US National Institutes of Health (NIH) free digital archive of biomedical and life sciences journal literature, 6 months after the publication date of the issue.

The authentic, final copy-edited version of authors' articles will be placed in PubMed Central without the need for further work from them.

George Banting (Bristol), Chairman of the Editorial Board, said 'this policy will provide an additional and independent secure online archive for the journal and serve to reinforce the journal's role as a major vehicle in the global communication of science'.

The Biochemical Journal, which celebrates its centenary in 2006, offers a reviewing process of 4 weeks for full papers (2 weeks for Accelerated Publications), 9 weeks from acceptance to publication online for full papers (6 weeks for Accelerated Publications) and accepted papers are published online as pdfs within 5 minutes of acceptance as Immediate Publications (IMPs).

Appetite, the gut and obesity

A modern tale of physiological endeavour from Stephen Bloom

Stephen Bloom

World-wide, over 150,000 people a month die prematurely from obesity. This massive number of unnecessary deaths rivals those directly caused by the catastrophic Boxing Day tsunami. Unlike the tsunami, it happens regularly and predictably, month after month, year after year. We have no medicines that are effective in treating obesity. Advice to stop eating and take more exercise has been dished out by doctors for the last 100 years – the only effect has been accelerating adiposity.

Modern man is a survivor of many famines. Malthus proposed that with no dominant predator, the numbers of a species would increase until the food ran out. Man is the top predator and his numbers have therefore been limited by food availability for aeons. Restrained eaters would sometimes starve to death. Only the greediest survived. This genetic legacy makes us voracious overeaters. In a modern world dripping with highly nutritious and easily available fast food which never runs out, only by the exercise of enormous will power do some of us keep our waist lines from expanding. This calorie rich environment combined with the lack of need for exercise is hog heaven for overeaters, and makes the current obesity epidemic seemingly inevitable. Faced with previous disease epidemics and natural catastrophes, man has successfully applied science as a remedy. We now need to apply science to reset man's inappropriate appetite, and to succeed we must understand how appetite is controlled. Physiologists to the rescue!

The first real breakthrough was the discovery of the appetite inhibiting fat hormone leptin. It was also the first big disappointment. Leptin has turned out to be only a reassurance factor, released from fat to tell the brain that you aren't starving to death. Thus if you loose your fat in a famine you have no leptin to reassure the brain. You can think only of food, all growth stops, menstrual cycles stop, and the immune system shuts down. Injecting leptin instantly restores all of these functions, without the need for any extra food. In contrast, giving fat people leptin doesn't reduce their appetite at all because the obese already have lots of leptin.

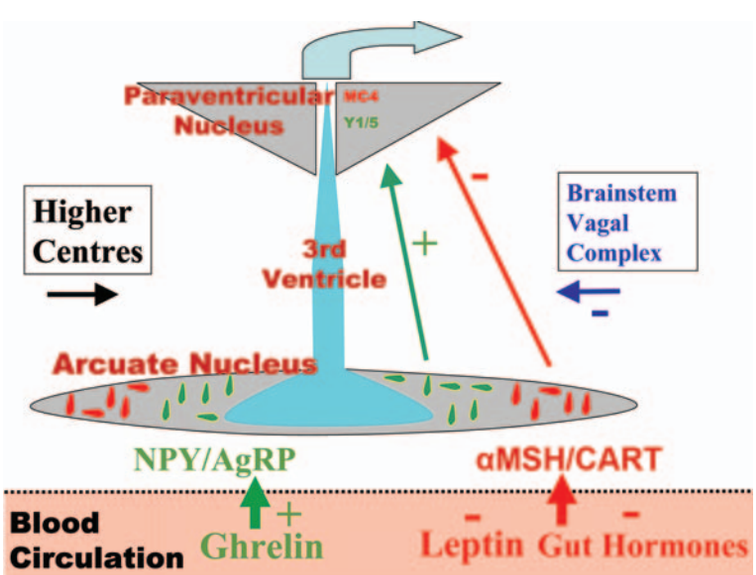


Figure 1. Eating and energy expenditure

But we can limit our hunger. Everyone feels less hungry after lunch. Why? It isn't the bulk. Just compare the effect on your appetite of eating two big chocolate bars or a pile of boiled cabbage – only the former assuages appetite. It isn't the rise in circulating nutriments because intravenous infusions of nutriments don't stop you feeling hungry. Actually it is likely that the loss of appetite after a meal is due to specific neural or hormonal gut signals to the brain. Eating releases a number of gut hormones, including oxyntomodulin, glucagon-like peptide 1 (GLP1), peptide YY (PYY3-36) and pancreatic polypeptide (Batterham *et al*. 2003; Dakin *et al*. 2004; Holst, 2004; Wynn *et al*. 2005). These hormones have been found to inhibit appetite. They also inhibit release of the 'hunger hormone' ghrelin. Ghrelin is a peptide hormone released from the endocrine cells of the stomach when you're hungry and ghrelin release is reduced after a meal (Wren *et al*. 2001). Thus gut hormones produce a co-ordinated satiety response.

These circulating peptide hormones penetrate the CNS in specific regions such as the area postrema and arcuate nucleus, where they affect the neuronal circuitry that regulates how hungry you feel. The central dogma of CNS appetite control is that the hypothalamic arcuate nucleus receives and coordinates signals giving information about the acute and chronic state of energy balance (Fig. 1). This nucleus contains two important types of neurone. One type stimulates appetite by releasing the neurotransmitters neuropeptide Y (NPY) and agouti-related protein (AgRP). The 'hunger hormone', ghrelin, stimulates this neurone, while leptin and the 'satiety gut hormones', PYY, GLP1 and oxyntomodulin, inhibit it. The second type of neurone inhibits energy

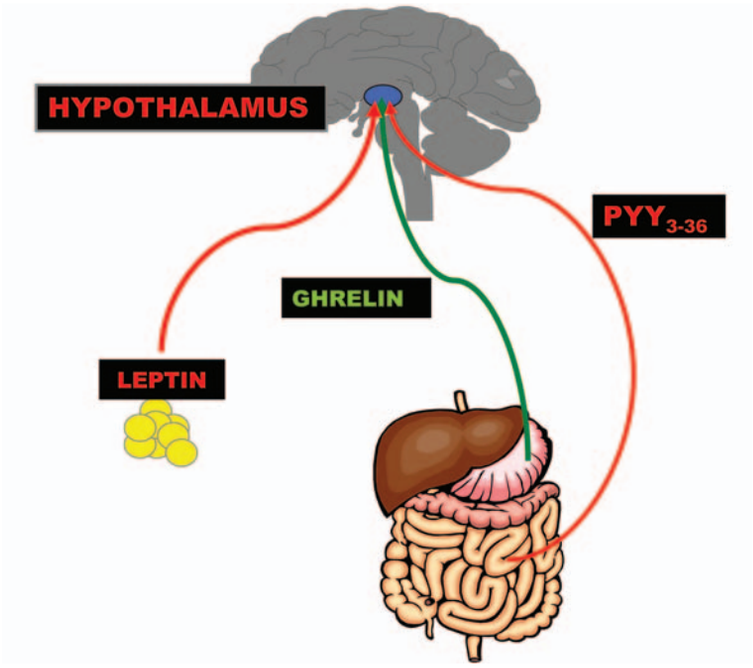


Figure 2. Peripheral signals regulating appetite

expenditure and appetite via the release of the alpha melanocyte stimulating hormone (alpha MSH), and 'cocaine and amphetamine related transcript' (CART). These hunger reducing neurones are inhibited by ghrelin but stimulated by leptin and the satiety gut hormones. Both the appetite-stimulating and appetite- inhibiting arcuate neurones project to another area of the hypothalamus, the paraventricular nucleus (PVN). The PVN is the 'motor nucleus' of the appetite system and is responsible for actually making you feel hungry or full and for burning off excess energy. If these gut hormones normally act on the brain to inhibit hunger after a meal, can giving them to the obese before meals make them lose appetite, eat less and thus lose weight? It has already been shown that artificial administration of these hormones to hungry volunteers inhibits hunger and decreases meal size. This specific physiological effect offers an exciting new way to regulate hunger and may lead to an effective way of treating obesity (Fig. 2). We can only hope that bigger and longer clinical trials show the inhibition of appetite by gut hormones to be both powerful and sustained. The benefits of such anti-obesity agents are potentially immense.

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See also the related article in our last issue (Trayhurn P (2005). Obesity – why all the noise? *Physiology News* **58**, 15.

*Alberto E Minetti, Convenor of the new Locomotion SIG (see article right) can be contacted at the Institute of Biophysical and Clinical Research into Human Movement at Manchester Metropolitan University, Cheshire, UK (*a.e.minetti@mmu.ac.uk).

To join the Locomotion SIG please contact Jamie Gould (jgould@physoc.org)

New Locomotion SIG

In the second half of the last century, particularly advantaged by emerging technologies in high-resolution dynamometry and digital motion capture, a new research field termed *Biomechanics* was inaugurated. While the remit incorporated a better understanding of the mechanics of living organisms and tissues, from actin-myosin complex to the entire body, locomotion was predominantly investigated at the start. Consistently stemming out from physiology at first, locomotion biomechanics is nowadays shared with biomedical engineering and the two research communities rarely gather to exchange and focus on integrative and comparative views on this topic.

The same applies to other researchers – anthropologists, neurophysiologists, exercise physiologists, zoologists, physiotherapists, theoretical biologists and robotics engineers – who increasingly deal with locomotion mechanics and physiology in their investigations. Opportunities to share knowledge of ongoing research would mutually enhance the awareness of the implications for cognate disciplines and allow scientists to better evaluate/predict the relevance of future investigations.

The new Special Interest Group (SIG) on Locomotion intends to focus on scientific contributions aiming to directly refer to, or shed light on, the final motor act, namely the body movement (normal, enhanced or impaired) in relation with the environment (land, water or air, normal or hetero-gravity) and time (locomotion evolution), spanning from the single cell to the whole organism, from simulations to optimization, in animals or humans.

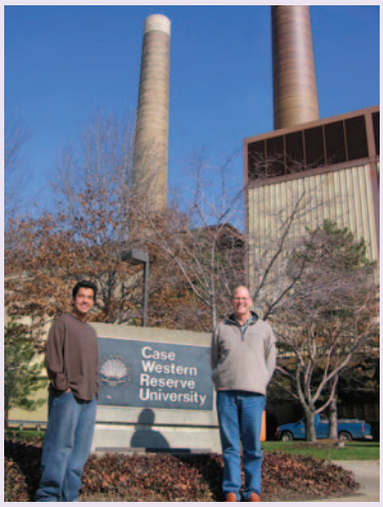
Through periodic thematic symposia, some in collaboration with existing SIGs, the Locomotion SIG will also attempt to generate 'bridges' between Physiological Society Members and other locomotion-oriented researchers in different associations, such as the International Society of Biomechanics (USA), the Society of Experimental Biology (UK) and the Society for Integrative and Comparative Biology (USA).

Also, a portal on the Society's website, where (frequently updated) references to the relevant literature about locomotion and some of the data made available by SIG contributors (from tables to multimedia material), will be downloadable. This initiative is meant to provide young researchers interested in locomotion with a 'guided' start into the subject.

Power and control: transferring energy when there is work to be done

The heart is all about power and control. The ventricles must generate sufficient power (i.e. cardiac output x developed pressure) to maintain blood pressure and organ perfusion, and this requires the controlled transfer of chemical energy to mechanical energy. This controlled transfer of energy is most evident with the transition from resting conditions to intense exercise stress: external power generation and myocardial oxygen consumption (MVO_2) increase 3 to 5 fold without ATP depletion or anaerobic metabolism. This is particularly impressive in light of the fact that cardiac ATP content is ~4 µmols g^{-1} and the ATP turnover at rest is ~0.25 µmols g^{-1} sec^{-1}, giving a mean turnover time of only ~16 sec at rest and ~3 to 5 sec during intense exercise. Simply put, production matches need, and the system is beautifully controlled.

How does cardiac muscle almost instantaneously accelerate the transduction of chemical to mechanical energy? ATP breakdown in the cytosol fuels contraction and relaxation, and it is matched by the oxidation of carbon fuels in the mitochondria, the generation of NADH and aerobic ATP formation (Fig. 1). Almost all of the ATP formation in the heart comes from oxidative phosphorylation, which is driven by the activity of complex V of the electron transport chain (ETC), the proton motive force across the inner mitochondrial membrane, and the availability of ADP and inorganic phosphate (P_i). The proton gradient is fuelled by the delivery of electrons (via NADH and $FADH_2$) to the ETC.



Naveen Sharma (left) and William Stanley

Studies in isolated mitochondria tell us that oxygen consumption and oxidative phosphorylation are turned on by an increase in [ADP] and the generation of NADH from carbon substrates, but what about *in vivo*?

It appears that [NADH] is kept constant with the transition from low to high work states due to the matching of NADH oxidation by complex I of the ETC with the rapid activation of substrate metabolism and NADH formation by pyruvate dehydrogenase (PDH), fatty acid â-oxidation, and the citric acid cycle (Fig. 2). We recently observed that with a 3-fold increase in MVO_2 in pigs there was activation of PDH, maintenance of [acetyl-CoA], and an increase in the concentration of citric acid cycle intermediates (Sharma *et al*. 2005). In fact, even when fatty acid oxidation was almost completely suppressed by pharmacological inhibition of mitochondrial fatty acyl uptake, there were no effects on [acetyl-CoA] or [NADH], MVO2 or cardiac power. Unlike contracting skeletal muscle, the myocardium is a metabolic omnivore, able to use glucose, lactate, pyruvate, acetate, fatty acids, and ketone bodies to generate NADH. Thus there is an inherent robustness to the system, guaranteeing a sufficient supply of reducing equivalents to the ETC regardless of the metabolic milieu.

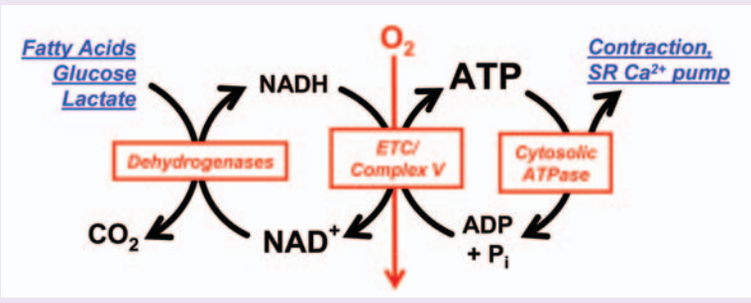


Figure 1. The rate of ATP breakdown is linked to ATP generation by oxidative phosphorylation, electron transport chain (ETC) flux, and NADH formation from oxidation of carbon fuels.

How is NADH generation activated with increased cardiac power and MVO_2? While PDH can be activated by classic substrate/product regulation via decreases in NADH/NAD^+ and acetyl-CoA/CoA-SH, none of these regulators are altered in the right direction when MVO_2 is increased *in vivo* (Sharma *et al.* 2005). On the other hand, *in vitro* studies show that Ca^{2+} activates PDH phosphatase (which activates PDH) and the citric acid cycle enzymes isocitrate dehydronase and α-ketoglutarate dehydrogenase (McCormack *et al.*1990), stimulating NADH generation. Moreover, there is an increase in intramitochondrial [Ca^{2+}] when there is an increase in extramitochondrial Ca^{2+}, such as occurs with adrenergic stimulation (McCormack *et al.* 1990). Thus the mechanism for activation of NADH generation with increased cardiac power is feed-forward stimulation of mitochondrial dehydrogenases via the transfer of cytosolic Ca^{2+} to the mitochondria.

If an increase in the concentrations of [NADH] and [ADP] are not responsible for turning on flux through the ETC and oxidative phosphorylation, then what is? One possibility is that increased [P_i] concomitant with accelerated ATP hydrolysis activates the ETC and complex V. Cardiac P_i levels are normally extremely low, and early studies in isolated mitochondria showed that P_i activates mitochondrial respiration (Chance & Williams, 1956). Recent studies in isolated pig heart mitochondria show that P_i activates complex I, electron flow, and complex

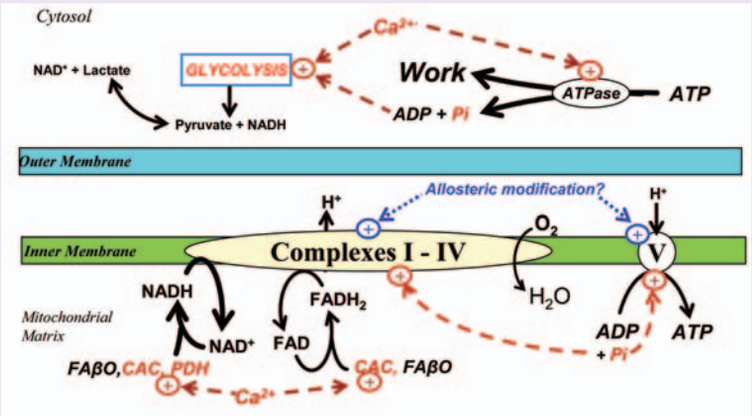


Figure 2. Schematic depiction of mechanisms regulating ATP generation during increased cardiac power (CAC, citric acid cycle; PDH, pyrvuate dehydrogenase; FAβO; fatty acid beta-oxidation).

V (Bose *et al.* 2003). Another possibility is that there is direct allosteric modification of proteins in ETC complexes that effectively increase the affinity for NADH and/or $FADH_2$. Evidence for this possibility comes from the recent observation that complex I from bovine heart mitochondria is phosphorylated in a cAMP-dependent manner (Chen *et al.* 2004). Further support for this concept comes from a computer model of oxidative phosphorylation, which found that only 'parallel activation' of ATP use and activity of the ETC complexes predicted experimental data during the rest-work transition in skeletal muscle (Korzeniewski, 2003).

There is a clear gap between our understanding of the *in vivo* activation of energy transduction with an increase in cardiac power, and the elegant biochemical mechanisms demonstrated in isolated mitochondria. *In vivo* studies are limited by the inability to measure key regulatory metabolites, particularly in the mitochondrial and cytosolic compartments, while *in vitro* results are generally limited by lack of physiological stimuli and inclusion of key cellular components. The goal is to understand how the system is regulated *in vivo*, however the system is too complex to process all of the information in one's head. Recent publications indicate that computer modeling of myocardial metabolic systems can provide a reliable method of predicting the metabolic response to stress both *in vitro* (Cortassa *et al.* 2003) and *in vivo* (Zhou *et al*. 2005), and elucidate physiological mechanisms that are not apparent solely through experimentation. Specifically, '*in silico'* studies allow for inclusion of fluxes within and among cellular compartments that cannot be quantified experimentally (Zhou *et al.* 2004). As metabolic models evolve in complexity, answers will be provided to elusive questions regarding the regulatory mechanisms that drive energy transfer in the heart under physiological and pathological conditions.

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Ageing influence on automatic movement

Tao Wu and colleagues focus on the understanding of motor control in normal and disorder conditions

Above, from left: Tao Wu, Piu Chan and Mark Hallett

Understanding ageing influence on human life remains a challenge. There is a series of changes during ageing, such as cell loss, synaptic degeneration, blood flow reduction and neurochemical alteration. Normal ageing is not only characterised by a decline of memory, perception and cognition, but also accompanied by progressive slowness and impaired motor ability. In recent years, functional neuroimaging techniques, like PET and functional MRI (fMRI), have been employed to compare brain activation in aged and young adults in performing memory, cognitive and motor tasks. Due to different paradigms used, and the different performance level aged subjects achieved, some results have been inconsistent. Most studies have focused on simple motor tasks, like finger tapping, and found that ageing subjects need greater activity and recruit additional brain regions for execution of certain tasks at the same level as young subjects. However, the influence of ageing on more complex motor behaviours has been only rarely studied. Actually, there is evidence which implies that normal ageing may have different effects on brain activity when performing various motor tasks.

In our recent work we used fMRI to investigate ageing influence on automatic movements (Wu & Hallett, 2005). Automatic movements are performed without attention being clearly directed toward the details of the movement, and automaticity is common particularly for movements

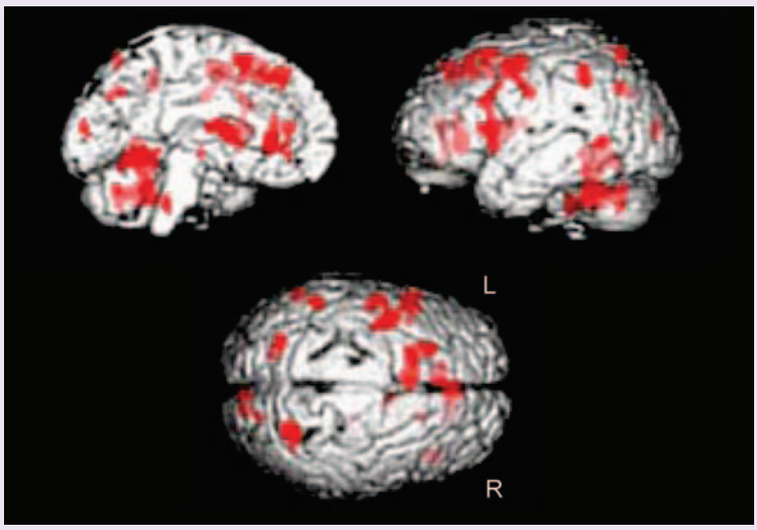

Figure 1. Brain areas more activated in aged subjects than in young subjects during automatic execution of sequence-12 ($p < 0.001$, uncorrected) (from Wu & Hallett, 2005).

that require low levels of precision or for movements that are frequently made (Bernstein, 1967). In a recent study on healthy young subjects we demonstrated that most of the motor network participates in executing automatic movements and that it becomes more efficient as movements become more automatic (Wu *et al*. 2004). There is evidence that aged normal subjects have more difficulty in achieving automaticity than young subjects (Rogers *et al*. 1994). However, the neural explanation of the problem has not been identified.

We asked aged healthy subjects to practice self-initiated, self-paced, memorised sequential finger movements with different complexity until they could perform the tasks automatically. Automaticity was evaluated by having subjects perform a secondary task simultaneously with the sequential movements. Although it took more time, most aged subjects eventually performed the tasks automatically at the same level as the young subjects. fMRI results showed that for both groups, sequential movements activated similar brain regions before and after automaticity was achieved. No additional activity was observed in the automatic condition. While performing automatic movements, compared to young subjects, aged subjects had less activity in the contralateral primary sensorimotor cortex (SM1), greater activity in the bilateral anterior lobe of cerebellum, premotor area, parietal cortex, left prefrontal cortex, anterior cingulate, caudate nucleus and thalamus, and recruited more areas, including the pre-supplementary motor area (pre-SMA) and the bilateral posterior lobe of cerebellum (Fig. 1).

These results indicate that most healthy aged subjects can perform some complex motor tasks automatically. The less activated SM1 in aged subjects suggests that unlike when performing simple movements, in which aged subjects could increase the utilisation of SM1 to maintain performance level and show greater activation in the SM1 than young subjects, for complex movements the activation in SM1 also significantly increased in young subjects, but in contrast, in aged subjects SM1 activity did not increase further. Therefore, SM1 in aged subjects was less activated compared to young subjects. Our finding of increased neural network activation for aged subjects is similar to previous observations on age-related changes in cognitive and motor circuitry. These extensively greater activated brain regions indicate that the strategy aged subjects use for execution of automatic movements is obviously less efficient. They appear to require more brain activity to compensate for the greater difficulty they have in performing automatically at the same level as young subjects. This appears to be the main reason why aged subjects have more difficulty in achieving automaticity.

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Look out for the Benevolent Fund stand at the meeting in July where we'll be raffling this wonderful prize, generously donated by the Society. That means every penny raised goes to the Fund and we can continue to provide grants to those encountering difficult financial circumstances. We have already provided £3000 in grants since the start of the year so every donation is vital. The Fund is there to help anyone employed in physiology, be they a lab technician, lecturer or cleaner (and importantly, their families and dependants) who is suffering financial hardship, perhaps due to illness or bereavement. We can assist with medical costs, childcare fees or extra tuition, emergency travel expenses or funeral arrangements and can act quickly in emergencies.

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Pharyngeal airway mechanics during muscle stimulation by tagged magnetic resonance imaging

A novel application of MRI tissue tagging was used to track tissue motion in the pharyngeal walls due to contraction of tongue protrudor muscles that dilate the airway. Airway enlargement in the antero-posterior and lateral dimensions was associated with ventrally directed displacement of the lateral and ventral pharyngeal walls. The results reveal complex relationships between changes in airway size and pharyngeal wall tissue motion

Obstructive sleep apnoea (OSA) is a respiratory disorder in humans characterized by the repetitive closure of the pharyngeal airway during sleep. It is widely acknowledged that both anatomical and physiological factors may predispose an individual to OSA. Schwab *et al*. (2003) have used magnetic resonance imaging (MRI) to show that patients with OSA have smaller pharyngeal airways and thicker lateral pharyngeal walls than individuals without OSA. While standard MRI techniques can determine airway dimensions and the geometry of pharyngeal wall soft tissue structures, they cannot directly examine pharyngeal mechanics, i.e. pharyngeal wall tissue motion.

Physiological factors include the function of skeletal muscles in the pharynx that dilate and stiffen the airway. Selective neural stimulation of pharyngeal dilating muscles during sleep has been studied as a possible treatment to prevent airway closure (Schwartz *et al.* 1996). Although previous studies in animals and humans have examined the increase in airway size and stiffness due to pharyngeal muscle stimulation, there is little information as to how activation of the pharyngeal muscles alters the soft tissues in the pharyngeal walls to effect these airway changes (Fuller *et al.* 1999; Kuna & Brennick, 2002).

To address these limitations, we have adopted a novel approach using MRI with spatial modulation of magnetization (SPAMM®) (Axel & Dougherty, 1989) to track tissue motion in the pharyngeal wall during muscle stimulation (Brennick *et al.* 2004). We examined how stimulation of the medial branch of the hypoglossus nerve, supplying motor output to protrudor (genioglossus and geniohyoid) and intrinsic tongue muscles, affects the displacement and strain of tissues surrounding the pharyngeal airway and how the pharyngeal wall tissue motion relates to changes in airway size and shape. Eleven Sprague-Dawley rats were surgically prepared with platinum electrodes for bilateral stimulation of the medial branch of the hypoglossus nerve, and images of the pharyngeal airway were acquired before and during stimulation using a spoiled gradient recalled imaging (SPGR) MRI protocol in a 4.7T magnet. Image analysis used customized software including optical flow displacement and finite element analysis.

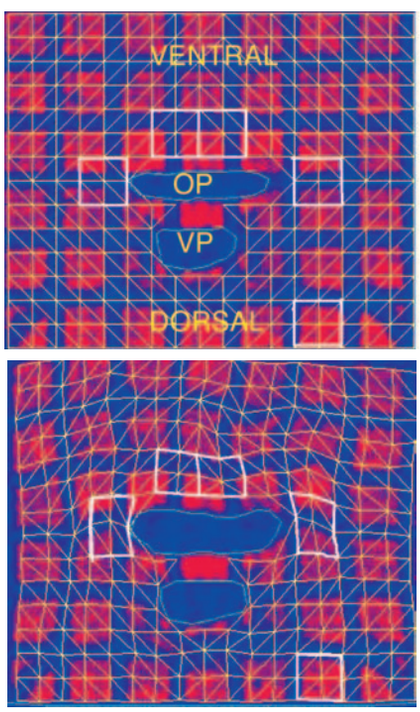

Figure 1. Pharyngeal airway wall sector strain and displacement. A representative axial slice from the caudal pharyngeal airway shows the pharyngeal wall tissue displacements with medial hypoglossal nerve simulation (top panel, before stimulation and lower panel, during stimulation). Optical flow methods were used to determine point to point tissue displacements and these points formed the vertices of the triangular mesh used in the finite element analysis. The images are annotated to show velopharynx 'VP' and oropharynx 'OP' and the ventral and dorsal directions. Strain and displacement variables were calculated from each of the four wall sectors selected bilaterally in the lateral and ventral pharyngeal walls and from a fifth sector, located in the brain tissue, that served as a control.

Airway dimensions measured before and during stimulation showed that cross-sectional area, and anteroposterior and lateral dimensions in the oropharyngeal and nasopharyngeal airways, were significantly increased when results were averaged across the rostral, mid- and caudal pharynx (p values <0.001).

Fig. 1 shows images of a single axial slice in the caudal pharynx before (top image) and during stimulation (lower image). Note the change from the perpendicular grid pattern prior to nerve stimulation (top panel) to the distorted pattern (lower panel) during stimulation. Pharyngeal wall tissue displacement and strain were

determined bilaterally in tissue sectors in the lateral and ventral pharyngeal walls surrounding the oropharyngeal airway and compared with a control sector in the brain.

Stimulation caused ventral displacement of tissues in the ventral pharyngeal walls in all regions ($p<0.0032$) and ventral displacement of the lateral walls in the mid- and caudal regions ($p<0.0001$) (Fig. 2). In addition, in the mid- and caudal regions, stretch (principal maximum strain) of lateral sectors was significantly greater than that of control sectors ($p<0.023$). As there was no lateral displacement of the lateral pharyngeal walls at any rostral to caudal pharyngeal level examined, these results suggest that airway dilation during stimulation of the medial branch of the hypoglossal nerve was predominantly due to ventral displacement of the ventral and lateral pharyngeal walls.

We believe this novel MRI application will lead to a better understanding of airway phenomena such as how dilator muscles act to maintain pharyngeal patency and how airway collapse occurs in different regions of the pharynx.

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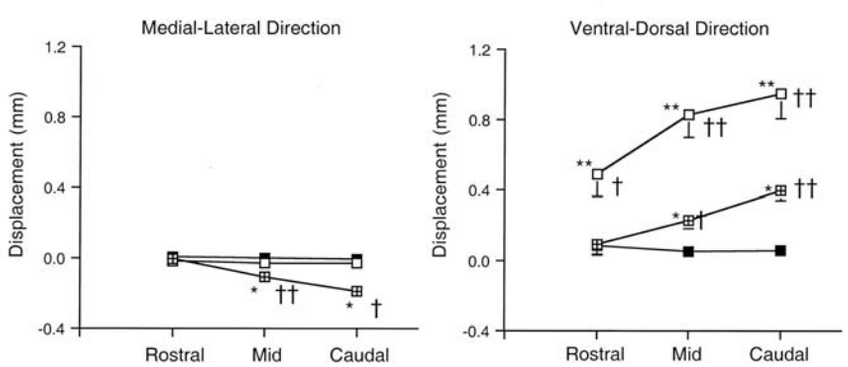

Figure 2. Pharyngeal wall tissue displacement.
Shown are mean (±SE) tissue displacements in the medial-lateral (left panel) and ventral-caudal (right panel) direction in the ventral (☐), lateral (crossed ☐), and dorsal (■) pharyngeal wall sectors in the rostral, mid- and caudal pharynx. In each plot, displacement (ordinate) represents movement of a right-sided pharyngeal wall sector relative to the centroid of the velopharynx, such that positive medial-lateral displacements were directed laterally, and positive dorsal-ventral displacements were directed ventrally. Note, in the left panel, the lateral sectors in the mid- and caudal regions showed significant ($p<0.0001$) medially directed displacement, and that medially directed displacement of mid and caudal lateral sectors, was significantly greater than both ventral and control (noted, *) and significantly greater in the caudal region (noted, †) than in the mid-pharyngeal region (noted, ††) ($p<0.016$). In the right panel, displacement in both ventral and lateral wall sectors was significantly greater than that in control (all p values <0.003) with ventral sector displacements (noted, **) greater than lateral sectors (noted, *). Other comparisons showed that displacements in mid- and caudal regions (noted, ††) were significantly greater than those in the rostral regions (noted, †) (p values <0.03).

New actions for familiar vasoactive signals

Recent studies reveal previously unrecognised roles for vasoactive signals in the retinal microvasculature. Donald Puro discusses the physiological and pathobiological implications

Donald Puro

A traditional notion of vascular physiology is that pericyte-containing microvessels, which are present in all tissues except the liver, play only a passive role in regulating blood flow. However, contrary to this idea it is now becoming clear that, by controlling the contractility of abluminally located pericytes, vasoactive signals can cause microvascular lumens to constrict or to dilate (Schonfleder *et al*. 1998; Kawamura *et al*. 2004). These observations point to a new paradigm in which local perfusion is regulated, at least in part, at the capillary level.

In the quest to understand how local perfusion is regulated, a number of investigators have focused on the retinal microvasculature, which is particularly well adapted for the local control of capillary function. One adaptation that facilitates local control is the retina's lack of autonomic innervation, which in other vascular beds allows extrinsic CNS oversight. In addition, the blood-retinal barrier created by tight junctions between vascular endothelial cells markedly limits the ability of circulating vasoactive molecules to affect perivascular contractile cells. Suggestive of the importance of pericytes in regulating local perfusion within the retina, the density of these

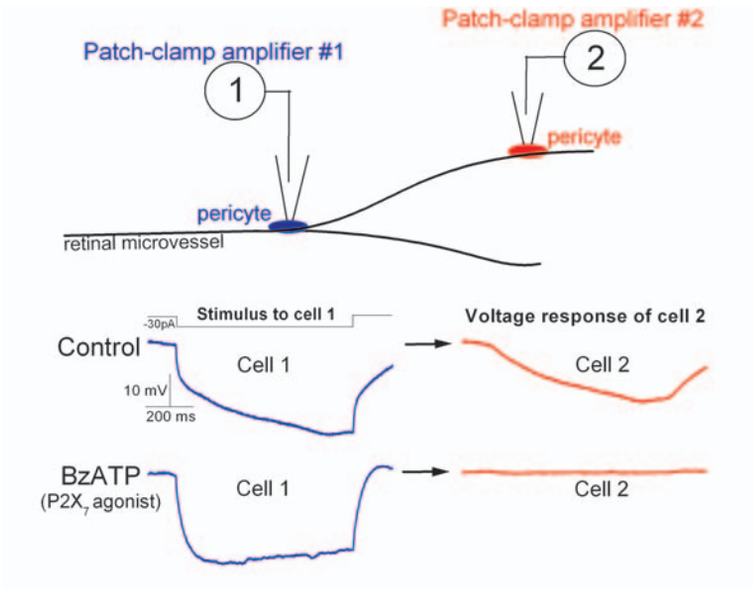

Figure 1. Inhibition of cell-to-cell coupling within retinal microvessels. The top panel is a schematic illustrating the positioning of two perforated-patch pipettes that were located 240 μm apart on a freshly isolated microvessel. A current step was applied to one of the sampled pericytes (cell 1), and the membrane potentials of both pericytes were monitored. Below are shown the voltage traces recorded in the two sampled pericytes under control conditions and during exposure to the purinoceptor agonist, benzoylbenzoyl-ATP (BzATP). From Kawamura *et al.* (2003) with permission.

cells is higher in this tissue than at any other site in the body.

An experimental advantage of studying the retinal microvasculature is the ability to isolate, from the adult rodent retina, viable complexes of pericyte-containing microvessels (Sakagami *et al*. 1999). This preparation allows investigators to monitor pericyte currents via patch-pipettes, measure pericyte calcium levels with fura-2, and visualize changes in pericyte contractility and lumen diameter by time-lapse photography. Using this new experimental approach, our laboratory has detected previously unrecognized actions of well known vasoactive signals.

Regulation of cell-to-cell communication

Experiments using freshly isolated retinal microvessels reveal that several vasoactive signals not only affect the contractility of individual pericytes, but also regulate the spatial and temporal dynamics of the vasomotor response (Kawamura *et al*. 2002, 2003, 2004). Angiotensin II, ATP and endothelin-1 potently inhibit cell-to-cell communication within microvascular complexes, in addition to evoking the release of stored calcium, activating non-specific cation channels and causing pericyte contraction (Fig. 1). The regulation of gap junction pathways is a newly appreciated mechanism by which extracellular molecules regulate microvascular function.

Almost certainly an inhibition of cell-to-cell transmission would profoundly influence how a microvascular complex responds to a vasoactive signal. For example, a localized exposure to angiotensin, ATP or endothelin would initially evoke depolarization throughout a network of microvessels as voltage changes induced by the opening of ion channels spreads electrotonically from cell to cell. However, when gap junctions close, intercellular transmission would cease. As a consequence, it is predicted that blood flow would be dynamically affected. Initially perfusion of a relatively large area of the microvasculature would be decreased, but subsequently the inhibition of blood flow would be delimited to the capillary segment directly exposed to one of these extracellular signals. Perhaps the transient inhibition of perfusion in upstream vessels allows for a rapid and effective decrease in capillary blood flow without resulting in a sustained and potentially harmful hypoperfusion of widespread areas within the retina.

Purinergic vasotoxicity

Recent studies indicate that extracellular ATP not only serves as a signal regulating pericyte contractility, but also can cause cell death in the retinal microvasculature. As shown in Fig. 2, this nucleotide activates two potentially lethal pathways (Sugiyama *et al*. 2005). Both pathways require the activation of $P2X_7$ purinoceptors whose activation not only opens the ligand-gated channels, but also can be associated with the formation of large transmembrane pores. These pores, which are permeable to molecules of up to 900 Da, can disrupt cellular metabolism and cause microvascular cell death. In addition to the opening of lethal pores, a cytotoxic response to ATP can occur when a $P2X_7$-induced depolarization activates voltage-dependent calcium channels (Fig. 2).

The discovery of the lethal effects of ATP in isolated retinal microvessels raises the possibility that endogenous vasoactive signals can also be vasotoxic. Although the idea that signaling molecules can cause cell death in the circulatory system is new,

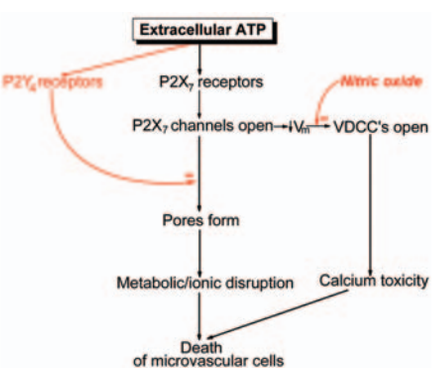

Figure 2. Purinergic vasotoxicity. Exposure of retinal microvessels to ATP activates $P2X_7$ and $P2Y_4$ purinoceptors. Secondarily, VDCCs can be activated by the $P2X_7$-induced depolarization. Shown in red are pathways that prevent ATP-induced cell death: $P2Y_4$ activation initiates a sequence of events that inhibit the formation of potentially lethal $P2X_7$ pores; nitric oxide prevents cytotoxic amounts of calcium from entering microvascular cells via VDCCs. From Sugiyama *et al.* (2005) with permission.

the concept of extracellular signals having both physiological and pathological effects is not novel. For example, in the nervous system it is well known that the excitatory transmitter glutamate can be neurotoxic. Analogous to excitotoxicity playing a role in neuronal pathobiology, purinergic vasotoxicity may be an important cause for microvascular dysfunction.

Because microvascular cell death has dire consequences for neuronal function, it would seem essential for purinergic vasotoxicity to be prevented in the normal retina. Consistent with this, ATP's lethality can be held in check by two mechanisms: a $P2Y_4$-mediated inhibition of $P2X_7$ pore formation and a nitric oxide-mediated inhibition of voltage-dependent calcium channels (VDCCs) (Fig. 2). A challenge for the future is to determine whether dysfunction of these protective pathways plays a role in sight-threatening microvascular disorders such as diabetic retinopathy.

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Muscle afferents, back again?

James Fisher and Michael White explain how afferent feedback from the exercising muscle can be modified in health and disease – and how recent research is helping us to understand the neurophysiological basis for these *in vivo* observations

James Fisher (left) and Michael White

Classically, the cardiovascular response to exercise is said to be governed by both central feed-forward and peripheral feedback mechanisms. During exercise, slowly conducting group III and IV muscle afferents are activated by mechanical and metabolic stresses placed on the muscle. These muscle afferents relay feedback to the cardiovascular areas of the brain stem and cause both an inhibition of vagal outflow and an excitation of the sympathetic nervous system. This feedback, together with central command, produces the increase in heart rate and blood pressure associated with exercise (Fig. 1).

Activation of muscle afferents is intimately involved in resetting and adjusting the sensitivity of the baroreflex during exercise. Whilst muscle metaboreceptor activation is known to increase baroreflex sensitivity, muscle mechanoreceptor activation decreases the sensitivity of the baroreflex (Carrington & White, 2001). An often overlooked effect of muscle afferent activation is the modulation of motor neurone excitability in the spinal cord, a factor which has major implications for those interested in the mechanisms of central fatigue (see Gandevia, 2001 for review).

Importantly, afferent feedback from the active muscle can be modified by factors other than simply exercise intensity, for example muscle fibre type, training status, mass and temperature (Fig. 2).

Studies in both animals and humans have shown that the pressor response, resulting from isometric exercise of muscle with a faster contractile

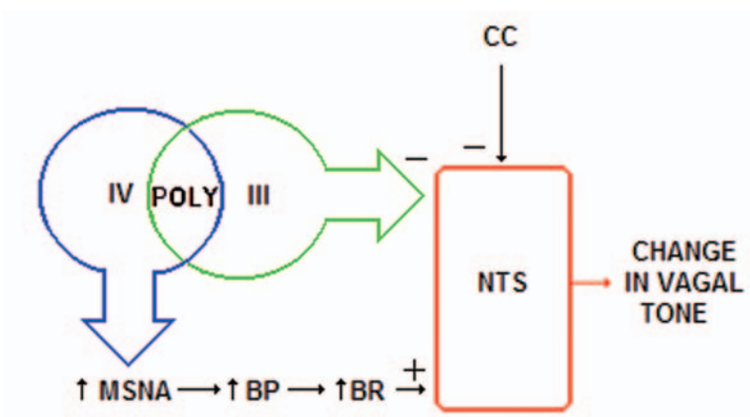

Figure 1. Hypothetical model illustrating how vagal tone is controlled during exercise by central feedforward and peripheral feedback mechanisms.
NTS, nucleus tractus solitarii; CC, central command; III, muscle mechanoreceptors; IV, muscle metaboreceptors; Poly, polymodal muscle afferents; MSNA, muscle sympathetic nerve activity; BP, blood pressure; BR, baroreflex; -, inhibitory effect; +, excitatory effect
(adapted from Fisher & White, 2004).

character and isomyosin content, is greater than that from a muscle of slower contractile character. This is because, for a given level of force production, fast fibres produce a greater metabolic stimulus to the muscle afferents. However, athletes who undertake training programs that place a high anaerobic load on specific muscle groups appear to attenuate this stimulus and have a smaller than usual pressor response to electrically evoked exercise of those trained muscle groups (Carrington *et al*. 1999). During electrically-evoked exercise there is no central command, so reduction of the exercise pressor reflex clearly indicates an attenuated afferent feedback. Similarly, longitudinal laboratory-based studies have shown that specific local muscle training also blunts the cardiovascular response to isometric exercise (Fisher& White, 1999). Thus it appears that training attenuates the stimulation of muscle afferents, either by reducing metabolite accumulation, or in some instances by blunting their sensitivity through chronic exposure to the products of anaerobic metabolism.

There may be surprising parallels between the local muscle conditions experienced by athletes training for longer sprint events (i.e. 400 m) and by the low-flow conditions in, for example, the muscles of chronic heart failure (CHF) patients. This might explain some similarities in muscle afferent-driven cardiovascular responses to exercise of their muscles. However even within the same muscle responses to mechanical or metabolic stress may be changed differentially due to training or disease. For example, Sterns *et al*. (1991) demonstrated that, when the muscle metaboreflex is activated in isolation by occluding the circulation to the forearm immediately after exercise, CHF patients show attenuated muscle sympathetic nerve activity compared with matched controls. As pH was found to be similar at this time, this suggests a desensitisation of the muscle metaboreflex. Furthermore, as muscle sympathetic nerve activity increased normally during exercise in CHF patients, there must have been an exaggerated contribution from either the muscle mechanoreflex or central command.

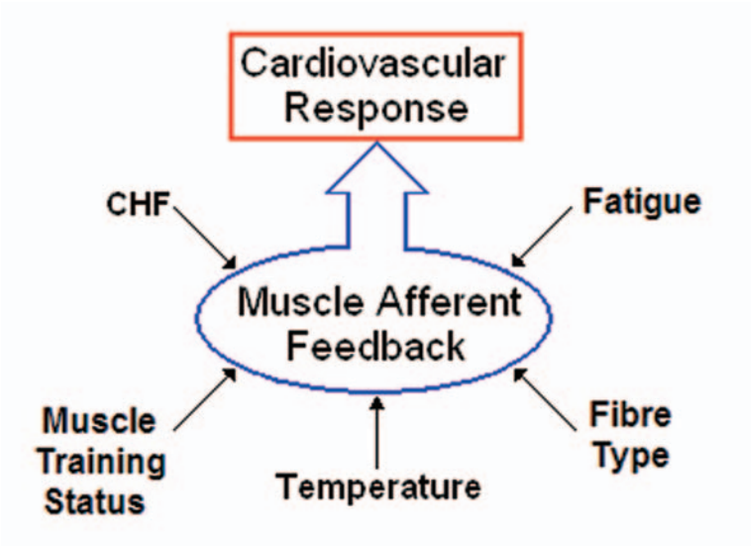

Figure 2. Factors affecting the magnitude of the muscle afferent feedback during exercise, and the resultant cardiovascular response. CHF, chronic heart failure

This complex situation may have been clarified in a recent study by Li *et al.* (2004) which suggests differential change in the sensitivity of specific receptors on muscle metaboreceptors (VR1) and muscle mechanoreceptors (P2X) in an animal model of heart failure. Whilst the sensitivity of VR1 receptors was blunted in heart failure, the sensitivity of P2X receptors was augmented. This is a major step forward in our understanding, as the properties of these receptors are well documented in vitro. For example, the activity of the VR1 receptor normally increases as pH falls and temperature rises. Of course, both of these changes occur in muscle during isometric or dynamic activity if the intensity is high enough or if blood flow is restricted.

How these receptors are affected in human muscle which has become adapted, or is undergoing adaptation, to altered activity pattern or disease is evidently an important question and one requiring an integrative physiological approach. It seems that – forgive the pun – the story of muscle afferents in human exercise physiology still has a long way yet to run.

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An unconventional marriage between physiology and art

A dual interpretation of the transition from sleep to wakefulness

To some, Science and Art would appear to be at opposite ends of the intellectual spectrum. Closer examination suggests that in many aspects these two disciplines are in fact inextricably linked. Both aim to explain or interpret particular phenomena of interest. Furthermore, both employ methodological frameworks that display as many similarities as differences. Science aims to answer questions using a systematic approach consisting of repeated observation. Similarly, artists must observe their subject over and over again to achieve their goal. The individual methods selected by both to achieve this, will have necessitated refinement over a significant period of time.

After the collection of observations in either a physical or intellectual sense, the next stage is one of interpretation. At this point the scientist or artist must 'make sense' of their observations. A scientist will become involved in a process of theory formulation or verification to describe the observed phenomena. An artist must find a way of putting their observations and interpretations into a visual language.

Both processes involve a considerable degree of creativity. In the case of the scientist this creativity may take the form of intuitive leaps that may deviate considerably from conventional theory. For the artist the language of interpretation must be relevant to the subject and be executed with expertise and originality. The product of such artistic enterprise is often striking and poignant, but to have value it must also in some way generate a meaning to the observer, thereby inducing a significant result. In scientific terms, both significant and non-significant findings have been used to explain or predict events. A quick glance at the history of science shows that the application of scientific discoveries has benefited the human race in myriad ways. Similarly, art has provided intellectual and emotional stimulation for many.

Figure 1. A series of videos of healthy subjects experiencing the transition from rapid eye movement (REM) sleep to wakefulness.

An interaction between art and science is one of the requirements for applicants submitting proposals to the Wellcome Trust for grants to support collaboration between science and art (Sci-Arts Projects). Mary Morrell (Senior Lecturer at Imperial College, London) and Catherine Yass (artist) were the recipients of Wellcome Trust funding in 2002 with a project, *Waking Dream*, that aimed to characterise the process of waking up from sleep and its impact upon the body and mind. Morrell adopted a physiological approach to quantify the process of waking from sleep, whilst Yass focused upon the subjects' perceptions of this experience. The combination of scientific and artistic analysis was used to challenge the viewer to participate in an enquiry regarding the definition of arousal from sleep, and how the analytical approach selected can influence the answer to the questions posed.

From a scientific perspective, the transition from sleep to wakefulness is of interest because to date a comprehensive understanding of this process has eluded scientists. For example, the precise alignment of wakefulness, consciousness and cardiovascular function remains unclear. Arousal from sleep is particularly significant because of its impact upon the cardiovascular parameters; surges in heart rate and blood pressure can occur that far exceed physiological requirements. From a clinical perspective, such surges negatively influence prognosis in those individuals with chronic illnesses such as sleep apnoea, respiratory or cardiac disease. In a series of studies in healthy subjects, Morrell's group have shown that the cardiovascular response to an arousal from sleep is not associated with changes in blood gases, upper airway reflexes, or the intensity of the arousal from sleep (O'Driscoll *et al*. 2004a; 2004b). These data support the suggestion that in healthy subjects the mechanism that produces the cardiovascular response is a fixed activation response, which is independent of respiratory stimuli (Horner *et al*. 1997; Horner, 2000). In patients with sleep apnoea, a homeostatic response to respiratory and possibly haemodynamic stimuli may be present at the time of arousal from sleep (Trinder et al. 2003). In this case the magnitude of the cardiovascular response would be related to either baroreflex activity, or a direct response

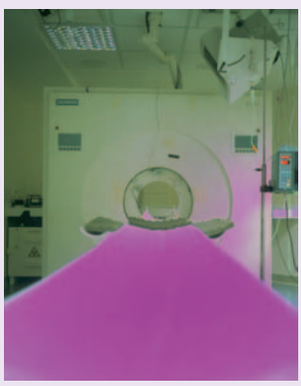
to respiratory stimuli. Furthermore, there may be clinical implications to the switching of mechanisms. The fixed activation response will dampen the magnitude of the response at high levels of stimulation, protecting the individual from excessive cardiovascular activation during arousal from sleep. In contrast, homeostatic control allows substantial activation in response to high levels of stimulation. Work in this area is ongoing in Morrell's laboratory.

From an artistic perspective Yass has had an ongoing interest in the role of the unconscious in shaping our perception of the waking, spatial environment. During the project Yass's practice evolved and developed. Initially, she recorded a series of videos of healthy subjects experiencing the transition from rapid eye movement (REM) sleep to wakefulness. She was interested in exploring the cross-over between sleeping and waking, and asking whether there is a moment when the subject is both asleep and awake at the same time, where dreams mingle with reality. The reader is invited to look at the images in Fig. 1 and consider whether they can separate the moments when the subject was awake or asleep.

The second part of *Waking Dream* focused on patients with parasomnia; including patients who walked during sleep. This enquiry considered states that are usually associated with wakefulness, which occur during sleep and are motivated by hidden or unconscious drives. A single male subject who had sleep walked all of his life agreed, with ethical approval, to participate. His responses during sleep in his own home were visually recorded over a 2 week period using a miniature infra-red camera attached to his head. It was hoped that this approach would enable the observer to view the process of waking and walking from the subjects' perspective rather than from a voyeuristic one.

Unfortunately, the nature of sleep is such that the camera was required to run for a considerable time, which meant that a large battery pack had to be worn by the participant. This disrupted the sleep pattern of the participant and it was decided not to continue with this part of the project.

The final part of the project involved Yass exploring images derived from her own dreams. Her interest lay in the limits of both artistic and scientific apparatuses to record experiences which have no physical manifestation. She chose to work with photography precisely because it is used in both art and science as a recording device, and to highlight the discrepancy between a medium associated with truth, and images which are illusions. Yass chose to reconstruct her dreams and 'photograph' them. Colours were manipulated by combining positives and negatives, and the prints were mounted onto light boxes, giving them an unreal, dreamlike quality. The photographs function as an archive of illusions, with no fixed meaning and open to any interpretation. (*This may at first seem different from the way evidence is gathered and assessed in science, but in both practices the same material can be interpreted differently in different contexts and times*.)



A PET scanner was used to investigate ways of scanning the brain. The scanner can appear to some as an alien image, perhaps from a dream.

Some of the aforementioned images are to be incorporated into a display at the Royal Brompton Hospital in London, where they will be seen by patients attending the sleep laboratory and by hospital staff and scientists working within the National Heart and Lung Institute at Imperial College. In this way the collaborators will showcase the results of this innovative science – arts project. It is anticipated that the display will generate conversation into the methods of analysis used and the nature of the subject.

In conclusion, this unconventional marriage between art and physiology provided an opportunity for those involved to approach a single question using very different methodologies. They found as many similarities as differences in their approach, particularly in the way that information is gathered and interpreted. Without doubt *Waking Dream* broadened their horizons and practice in ways that could not have been anticipated at the start of the project.

Acknowledgements

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Neuroscience by the sea

Thelma Lovick reports from the BNA national meeting

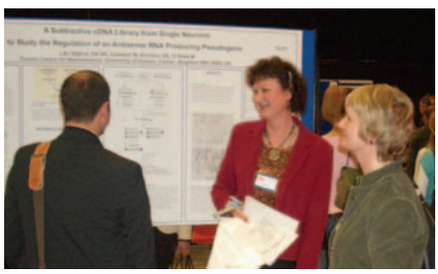
The British Neuroscience Association has come a long way since the days of its humble origin as the Brain Research Association, whose meetings were traditionally held in various university cities in a pub over a few beers. Whilst local meetings still continue, although not always in pubs these days, a national meeting has now become a firm fixture on the calendar of British neuroscience. They are held on a biennial basis, alternating between meetings of the Federation of European Neuroscience Societies, whose venue shuttles around various major European cities. The next FENS meeting will be held in Vienna in 2006.

After several years of taking the waters in Harrogate, the BNA moved its 18th National Meeting on 3-6 April to Brighton. The Brighton Centre provides an excellent venue right on the sea front with spacious accommodation, including several lecture theatres in close proximity to each other. There is ample space for comfortable viewing of posters as well as the accompanying trade exhibition, which this year included a flock of tiny stuffed sheep which had managed to stray onto every stand by the final morning! As usual, this BNA meeting was well organised, even down to details such as the weather. After a little sea mist in the morning, fine spring weather prevailed, so that a turn along the promenade could combine a constitutional walk with the opportunity for earnest scientific discussion or simply be used as a means to blow away any cobwebs hanging over from the night before. On the final morning the appearance of a stiff breeze along the sea front and crashing waves signalled it was time to go home. Yvonne Allen, the BNA Executive Secretary, must surely take much credit for organising the impeccable timing!

The British Neuroscience Association now boasts some 2,000 paid up members, of which just over 600 delegates came to Brighton. As in the past, this was a 'young' meeting, with most of the posters being presented by postgraduate students and post docs. It says much for the stamina of these younger scientists that the final session, with an 8.30 a.m. start on the morning after the traditional BNA 'bash', was still quite lively. Each day started and concluded with a plenary lecture. The rest of the day was taken up with two poster viewing sessions interspersed between morning and afternoon symposia slots. Since five symposia ran in parallel, there was plenty to do and plenty of good quality science to choose from!

Where is British Neuroscience going? Well according to Jim McCulloch it is not likely to be going down the cerebral ischaemia route for much longer. In a pithy lecture he showed that the promising leads, which arose from the intensive research effort of the past 15 years, have summarily failed to come up with an effective therapy for stroke. As a consequence, industrial money is drying up. Even so, exciting advances are being made in the field of cerebral blood flow and metabolism as demonstrated in Pierre Magistretti's opening lecture, so this may be an over pessimistic view. The pain field, which was not particularly well represented in Brighton, possibly due to the imminent meeting of the International Association for the Study of Pain in Sydney, found itself in a similar situation a decade ago. However, perseverance seems to have paid off and the development of a new generation of analgesic compounds and analgesic strategies has lead to improved pain relief.

Perhaps the excitement of this year's meeting was provided by the advances in the field of stem cell biology and in a greater understanding of degeneration and repair processes. Neuronal plasticity also featured strongly. It is clear that the concept of a hard wired brain, which still features in many textbooks, is both naïve and outdated. We appear to be working with an organ that is in a constant state of flux. Its study therefore may be more difficult but also so much more intriguing.



Top: Pierre Magistretti (left), this year's Wolstencfort Lecturer, with Thelma Lovick (far right) and members of the Wolstencroft family: Hisako Ikeda Wolstencroft (in foreground) with Helen Wolstencroft and partner Martin (behind).
Centre: Yvonne Allen and Debbie Dewar at the posters.
Above: A flock of tiny stuffed sheep graced the trade exhibition.
Below, left: Brighton pavillion.

As with most meetings, much of the scientific interaction goes on over coffees and beers. Indeed, networking is an important aspect. What did I pick up on the grapevine? A lot of discontent with perennial funding problems, despair about the scarcity of good post docs, frustration with the RAE and how it has become the force that drives university research 'strategists' at the expense of more creative, higher risk science. But it was not all negative. I personally made new contacts and renewed old ones and came away with new ideas and possibilities for future collaborations and, of course, I picked up a whole lot of new gossip that cannot possibly appear in print!

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The Northern Cardiovascular Research Group

The annual Northern Cardiovascular Research Group meeting took place on 14 January in Liverpool. This Group has been meeting for some 15 years now, and has traditionally involved those with an interest in cardiac and vascular smooth muscle from the universities of Liverpool, Manchester and Leeds. More recently, the net has been spread wider, and participants have attended from as far south as Oxford, and as far north as Glasgow. However, despite a few half-hearted attempts to change it to something more appropriate, the Group has retained its original title.

The meeting involved around 60 participants and was held in the beautiful Georgian Liverpool Medical Institute. The day began with a note of excitement as George Hart (one of the local organisers) accounted for the absence of Munir Hussain (the other): he had become a father some 4 hours previously.

Photo courtesy of Liverpool Medical Institution

Liverpool Medical Institution, venue for the Northern Cardiovascular Research Group annual meeting

The majority of the day was taken up with a series of 10 minute presentations. One of the main foci was regulation of intracellular Ca^{2+} in the mammalian cardiac cell. Gillian Graham (Leeds) began the proceedings by showing how, in papillary muscle maintained in culture conditions, the expression of a range of proteins which regulate intracellular Ca^{2+} is increased by raising extracellular [Ca^{2+}]. Fabien Brette (Leeds) illustrated the importance of the dyad (interaction between L-type Ca^{2+} channel and ryanodine receptor) for Ca^{2+} spark occurrence using a technique which removes the t-tubular portion of the sarcolemma of single myocytes. Zhaokang Yang (Leeds) and Stephen O'Neill (Manchester) focused on changes in the regulation of sarcoplasmic reticulum (SR) Ca^{2+} release in disease. Zhaokang's data was concerned with mutations in the ryanodine receptor which are associated with arrhythmogenic right ventricular dysplasia and catecholaminergic polymorphic ventricular tachycardia. He used a peptide which restricts the normal interaction of the central and N-terminal portion of the molecule, mimicking the effects of mutations which promote the open state of the channel. Later, Stephen O'Neill proposed an elegant mechanism for alternans at the level of the single myocyte involving the oscillating relationship between SR Ca^{2+} content and the threshold for Ca^{2+} wave propogation.

For those of us with an interest in SR Ca^{2+} release, all was not cardiac, and all was not mammalian. Ludmila Borisova (Liverpoool) showed the effects of ryanodine on Ca^{2+} signaling in endothelial and smooth muscle cells of terminal arterioles. Holly Shiels (Manchester) convinced a lecture theatre full of mammalian physiologists that fish are interesting, by relating the morphology and sarcolemmal structure of trout ventricular myocytes to temporal and spatial properties of the Ca^{2+} transients in these cells.

Integrating Ca^{2+} release into other aspects of excitation-contraction coupling (and returning to the mammalian heart), Norbert Szentandrassy (Manchester) described the acute effects of the polyunsaturated fatty acid, EPA, on Ca^{2+} handling and electrophysiology. Katherine Dibb, also from Manchester, presented data from a study looking at the effect of ageing (in sheep) on several aspects of excitation-contraction coupling. Given that age is a significant risk factor associated with the incidence of sudden cardiac death, it is interesting to see the potentially arrythmogenic changes in the action potential and Ca^{2+} transient that occur in these elderly animals.

Three talks of the day concerned mathematical modeling of pharmacological or physiological processes. Martin Leuwer (Liverpool) put forward an improved equation to describe the binding of local anaesthetics to the voltage operated Na^{+} channel, suggesting evidence of co-operativity. Our most southerly participant, Gentaro Iribe (Oxford) showed how a modification of the sarcoplasmic reticular Ca^{2+} handling parameters in a model of the cardiac cell enabled experimentally obtained characteristics of short-term force-interval relations to be reproduced. Vadim Biktashev (Liverpool) added to our understanding of arrhythmia by his presentation of a visually engaging model of human atrial tissue, illustrating the dissipation of fronts and self-termination of re-entrant waves.

Focusing for a change on non-myocytes, Karen Porter (Leeds) highlighted the role of the fibroblast in the pathological process of cardiac remodeling. Although statins are used clinically to lower blood cholesterol, Karen's data show that they also inhibit TNF-α induced fibroblast proliferation and invasion, with potentially cardio-protective consequences.

One of the highlights of the day was the guest lecture by Jean-Jacques Mercadier from Paris, France. He talked primarily about changes in expression of the sarcoplasmic reticular and sarcolemmal Ca^{2+} ATPases following myocardial infarction (MI), and the role that these play in arrhythmogenesis and remodeling. Transgenic animals overexpressing SERCA2 have been shown to be much more susceptible to arrhythmia but only during the 24 h period post-MI. These early arrhythmia are due to ischaemia, by contrast to those 48 h after MI which are caused by re-entry mechanisms. The consequences of overexpression of the plasma membrane Ca^{2+} ATPase (PMCA) were also discussed. Both NO synthase 1 and adenyl cyclase can be modulated by PMCA expression because of their Ca^{2+}-sensitivity; an effect which is enhanced by co-localisation of these components within caveolae, small invaginations of the cell membrane.

A very interesting day, fuelled by lively and informal discussion between presentations, was concluded by a meal in the Medical Institute. This meeting was made possible, in part, by generous funding from the Physiological Society.

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Cell volume and resting membrane potential

Fraser and Huang's article 'The interdependence of cell volume and resting membrane potential' (Fraser & Huang, 2005) is a perfect example of the spiral nature of scientific research. In 1972 the late Ichiro Matsubara and I published a paper on X-ray diffraction on skinned single fibres of frog skeletal muscle (Matsubara & Elliott, 1972). We had observed that the constant-volume nature of the myofilament lattice, first recorded by Hugh Huxley (Huxley, 1952) and confirmed by ourselves (Elliott *et al*. 1963), was lost when the muscle fibre was skinned, removing the cell membrane. To explain the constant-volume behaviour we used exactly the same equations as Fraser and Huang now invoke (see the Appendix to our paper). We used the Donnan relationship explicitly, rather than implicitly as Fraser and Huang do in writing that 'chloride is distributed passively'. We showed that constant volume was equivalent to constant charge concentration contained within the cell, and drew attention to the importance of the high negative fixed charge on the muscle structural and other cellular proteins. Our final Equation (vii) includes these parameters and gives the swelling pressure across the cell membrane in those terms. We called the charge valences Z_A and Z_B, because we chose to differentiate between the structural proteins [A] and other impermeable components [B]. We concluded that, as long as the total impermeable anionic charge within the cell membrane remained constant, any perturbation of the cell volume (stretching the muscle, for example) would be reversed by the operation of the swelling pressure. In fact this is an example of Le Chatelier's principle.

We were primarily interested in the volume of the cell, and we did not re-cast our equations to bring out the resting membrane potential explicitly, though this was implicit in the analysis. We cannot, though, claim to have been the first to use these ideas, Andrew Huxley (who as far as I remember refereed our paper for the *Journal of Molecular Biology*) pointed out that similar ideas appeared in a review by Boyle and Conway written some 30 years earlier (Boyle & Conway, 1941). We acknowledged their review in our paper (Matsubara & Elliott, 1972).

I realised at the time that when the muscle-cell membrane is removed the structural proteins stay put, keeping their fixed surface charge. Thus the same equations should still apply, *mutatis mutandis*, and the question was where the dominant phase boundary would now be. It quickly became clear that it was now around the A-band, and from constant charge-concentration in the whole cell we now had constant charge-concentration within the A-band, which explained the experimental X-ray results adequately. I published this interpretation the following year (Elliott, 1973) in a special issue of *J Mechanochemistry* produced in memory of Aharon (Katzir) Katchalsky, a great pioneer of polyelectrolyte physical chemistry who was tragically slain in the 1972 Lod Airport massacre. The paper included an estimate of Z_A, about $2\text{-}4 \times 10^4$ negative charges for each protein filament in striated muscle.

I was sad that Ichiro did not join me as a co-author of the *J Mechanochemistry* paper. Unfortunately, we had had some problems with one muscle editor who did not understand elementary physical chemistry and as a consequence Ichiro thought that he would lose face in the Japanese scientific community if he co-authored a paper that asserted that Donnan equilibrium could be set up without a membrane! Instead, he gave me a pair of silver and pearl cuff links that I wear to this day on those rare occasions when I put on posh clothes.

At around the same time Collins and Edwards showed that KCl-filled microelectrodes could be used to measure Donnan potentials in skinned muscle (Collins & Edwards, 1971), giving a direct estimate of filament charge. I followed this path for the next twenty years in collaboration with Else Bartels. We learnt much about electrical charge on the muscle filaments, including the striking experimental fact that stochiometric ATP decreases the negative charge on each myosin molecule by about 30%, from 115 to around 80 unit charges (Bartels *et al*. 1993). This did not make much impact in a field whose attention was focussed elsewhere, but I remain convinced it will prove to be important when the whole picture finally becomes clear. The charged polyelectrolyte approach also illuminated work on the structure and swelling properties of corneal stroma that I had initiated in the early 1970s with Julia Goodfellow, though that is a different story (see Elliott & Hodson, 1998).

In conclusion, it is good that the fixed charge on the impermeable anions in muscle is again the subject of research, and I wish Fraser and Huang every success in their work.

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Sir John Vane FRS

1927 – 2004

John Vane, who died peacefully of pneumonia on 19 November 2004, was heir to the physiological tradition of pharmacology and one of its greatest exponents. However, he became a biological scientist essentially by accident. His first choice of career, stemming from a childhood hobby, was chemistry and he graduated from the University of Birmingham with a Bachelors degree in that subject in 1946. But John, who was an experimentalist by nature, did not find the actual practice of chemistry as rewarding as he had imagined. Discussing his future with his head of department, he was told that J H Burn in Oxford was seeking graduates to be trained in pharmacology. John later wrote 'without hesitation I grasped the opportunity and immediately went to the library to find out what pharmacology was all about!' The study of experimental pharmacology turned out to be exactly what he was looking for and he never forgot Burn's inspirational early influence on his work and thinking.

After qualifying, John spent a short time at Sheffield University before returning to Oxford for postgraduate studies with G Dawes. In those days it was common for post doctoral scientists to do a stint in the USA and after receiving his DPhil John was invited by A Welch to join the Department of Pharmacology at Yale as an Assistant Professor. These early years were formative ones for John and one may trace the roots of much of his subsequent work back to these early influences and to the friendships he forged at this time.

In 1955 John returned to the UK and embarked upon what might be regarded as the first of his three major creative periods. He joined WDM Paton's Department of Pharmacology at the Institute of Basic Medical Sciences which was (after some time at Queens Square) located at the Royal College of Surgeons of England in London. John rose quickly through the academic ranks gaining a personal chair himself in 1966. GVR Born, a friend of John from his Oxford days, had succeeded Paton in 1961 and under the joint influence of Born and Vane, the department at the Royal College provided an astonishingly productive intellectual environment which published much cutting edge science, nurtured many careers and rose to great prominence.

It was during these years that John perfected his signature 'blood bathed organ cascade'; a combination, and a development along extraordinary lines, of JH Gaddum's parallel bioassay and superfusion techniques of 1953. Blood from animals, or sometimes humans, was passed continuously over a series of isolated tissues chosen for their exquisite sensitivity to, and ability to differentiate between, hormones or other substances under investigation. This technique enabled John to measure instantaneously and with great specificity, the levels of one or more blood hormones. The dynamic nature of this technique suited his temperament for insights and ideas came quickly to him and he was impatient to test them.

When animal blood was used it could be sampled from many different sites in the body and recirculated into the venous return enabling John to pinpoint the organs responsible for the release and removal of hormones such as angiotensin and bradykinin. Working on this problem with SH Ferreira, YS Bakhle and others he observed that the pulmonary circulation was a major site for the destruction of bradykinin as well as for the conversion of angiotensin I to angiotensin II. The group speculated that both phenomena were attributable to the same enzyme and deduced that the 'bradykinin potentiating factor' from *Bothrops jararaca* venom, which inhibited bradykinin proteolysis, might also block angiotensin I conversion and furthermore, that this strategy could prove a useful therapy for hypertension. John took the idea to Squibb where Welch, John's mentor from Yale, was by then Research Director. The outcome of this initiative was the development of the revolutionary ACE inhibitors.

A few years later, in 1971, John began what is generally regarded as his finest piece of work. Aspirin was a drug that had been around since the end of the 19th century, but for all its utility it had defied every attempt to unravel the underlying mechanism that linked together its distinctive therapeutic and side effects – a pharmacological profile that was also shared by many other 'non-steroidal anti-inflammatories'. John's interest in prostaglandins had been kindled some years earlier and

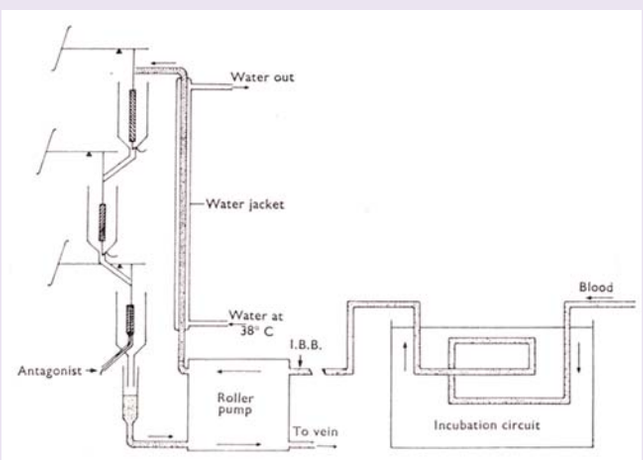
John Vane, pictured at the Royal College of Surgeons (then in Lincoln's Inn Fields) in the late 1960s with an old-fashioned kymograph.

John Vane in 1982, shortly after the announcement of his Nobel Prize, in front of one of his famous cascades.

over a weekend he conceived the notion that perhaps aspirin worked by inhibiting the generation of these multi-faceted mediators. He turned again to his bio-assay system for the answer and within a few days he had convinced himself and his colleagues that this indeed was the missing mechanism of action. This concept, which he further expanded mainly with Ferreira, S Moncada and RJ Flower, profoundly influenced the field including (in the 1990s) the development of Cox-2 inhibitors.

1973 saw a change in John's circumstances. Born had taken a chair in Cambridge and John was offered the position of Group Research and Development Director of the (then) Wellcome Foundation, in Beckenham, Kent. In those days 'The Foundation' was a unique institution; a pharmaceutical company whose profits were gifted to the charitable Wellcome Trust. Perhaps John was encouraged to accept this post by the thought that Sir Henry Dale, one of his intellectual heroes, was recruited by Henry Wellcome and was crucial to the early development of the company.

The 13 years that John spent at Wellcome presented him with a new and different set of challenges. He had no more time for lab work as such but continued to exert his influence on research in different ways. John had very definite views about drug discovery believing that if you recruited the most motivated scientists and allowed them to work on problems of their own choice in a well supported environment, then new ideas about disease mechanisms and ultimately new drugs would inevitably ensue. To implement this vision he took Ferreira, Moncada, Flower, GA Higgs and others with him to form a nucleus of his personal research group. In 1976, working mainly through Moncada, R Gryglewski and S Bunting, John's group discovered the potent vasodilator and anti-aggregatory prostaglandin 'X'. The mystery substance was characterised in collaboration with Upjohn and renamed *prostacyclin* (PGI_2). Analogues were later approved for the treatment of pulmonary hypertension and antithrombotic indications. Under John's management, Wellcome produced several other important drugs including Zovirax, Tracrium and Lamictal.



Schematic diagram of the blood-bathed organ cascade. This diagram first appeared in John Vane's 1968 Gaddum Memorial Lecture to the Pharmacological Society* and was later reproduced by Vane in his Nobel lecture. The cascade can also be seen in the picture of John Vane, above.
(*Reprinted by permission from *Br J Pharmacol*. Vane JR (1969). *Br J Pharmacol* 35, 209-242. Macmillan Publishers Ltd).

By now, John's contributions to his discipline were increasingly recognised. In 1974 he was made a Fellow of the Royal Society, in 1977 he won the Albert Lasker Basic Medical Research Award and in 1982 he shared with B Samuelsson and S Bergström, the Nobel Prize for Physiology or Medicine for his work on aspirin. In 1984 he was knighted in the New Years Honours list for services to pharmaceutical science. Over 50 other honorary degrees and fellowships followed over the years.

In 1986, aged 59, John left the Wellcome Foundation but the idea that he might simply retire and enjoy the fruits of a life's work was simply not an option for him. An invitation from St Bartholomew's Hospital Medical School, brokered by another old friend D Willoughby, coupled with an offer of some start-up funding from Glaxo Group Research, gave John the opportunity to start up a new lab; he accepted this challenge with alacrity thereby initiating the third major phase of his career. As always when starting a fresh venture, John's technique was to surround himself with colleagues that he trusted and respected and to work together with them to build up a critical mass of talented researchers. Groups headed by E Änggård, N Benjamin, I MacIntyre, D Tomlinson, B Whittle and Willoughby, as well as old colleagues Born and Flower, joined with John to promote his vision of a free-standing Institute devoted to excellence in inflammation and cardiovascular

research. From this confluence of research groups arose *The William Harvey Research Institute*. Major funding from Ono Pharmaceuticals in Japan enabled the institute rapidly to expand and it soon became a veritable powerhouse with a staff of over 120 people.

John himself, whilst rarely doing lab work, continued to influence the direction of the science focusing again mainly upon hormones influencing the heart and blood vessels as well as on the pharmacology of the Cox-2 inhibitors. He even found time to start up (with Änggård) a new company, *Vanguard Medica Ltd* (now *Vernalis*). He retired as full-time Director of the Institute in 1995 but still maintained his office and continued to influence the course of research and to direct young people. Following the merger of the Institute with the medical school in 2000 John took over the role of Honorary Chairman of the charitable *William Harvey Research Foundation*.

In getting to know John, there inevitably came a point when one was introduced to his family. John had married Daphne during their Oxford days where their two daughters, Nikki and Miranda, had also been born. Although by nature rather a shy man, John was immensely sociable and, together with Daphne and his daughters, frequently entertained friends and colleagues at their home, in restaurants and at scientific meetings around the world. Such parties were legendary and always carried off with enormous panache. Close colleagues were adopted by the Vanes as a sort of extended family which burgeoned as they made many life-long friends. Whenever scientists get together they like to discuss data, experiments and ideas which often make dull listening for others. But if this bothered Daphne, with her background in the liberal arts, she never showed it and always treated John's colleagues with great grace and charm. John was devoted to his 'girls', as he called them, and they provided the strongly supportive base from which he was able to launch his frequent and punishing schedules of work and travel.

John Vane's speech at the Nobel Banquet December 10, 1982

'Your Majesties, Your Royal Highnesses, Ladies and Gentlemen...

It is sometimes said that the major discoveries have already been made and that there is nothing important left to find.

This attitude is altogether too pessimistic. There are plenty of ideas and plenty of things left to discover. The trick is to find the right path from one to the other. The medicines of today are based upon thousands of years of knowledge accumulated from folklore, serendipity and scientific discovery. The new medicines of tomorrow will be based on the discoveries that are being made now, arising from basic research in laboratories around the world. Fundamental discoveries can and should be made in industry or academies, but to carry that knowledge forward and to develop a new drug to the market has to depend on the resources of industry. In many countries now, research in universities is under severe financial restraint.

This is a short-sighted policy. Ways have to be found to maintain university research untramelled by requirements of forecasting application or usefulness. Those who wish to study the sex-life of butterflies, or the activities associated with snake venom or seminal fluid should be encouraged to do so. It is such improbable beginnings that lead, by convoluted pathways, to new concepts and then, perhaps some 20 years later, to new types of drugs.'

(Reprinted with permission from the Nobel Foundation)

Science, with its uncompromising regard for facts and evidence rather than beliefs, is one arena where people can truly work together unhindered by considerations of race, colour, creed or gender. Like most scientists John was a committed internationalist in this respect. His labs were full of researchers from around the world and UK scientists usually constituted a minority. Of particular significance was John's relationship with the Polish scientific community which began in the late '60s during the cold war era. John made many trips to Poland during those difficult times, often taking hard-to-obtain scientific equipment and reagents with him and offering Polish scientists the opportunity to visit the West and to work in his laboratory. He made many close friends there and visited the country each year, invariably accompanied by Daphne, to attend scientific meetings. In 2003, John was accorded a rare honour in recognition of his contributions to the Anglo-Polish scientific collaboration when he was awarded the Polish Order of Merit at a ceremony in Warsaw.

As in many fields of medical research, John's own studies often depended upon laboratory animals. This drew unwelcome attention from the animal rights extremists who, being humanitarians, pursued a particularly vindictive campaign against him. Hate mail was sent; fire bombs thrown at his house; graffiti was daubed on out-buildings. These terror tactics did not deter him from his work and he was always an eloquent advocate for the responsible use of animals in scientific research and a source of moral support to others who had suffered in a similar way. He would have been very gratified by the efforts now being made by the BPS, the Physiological Society and the pharmaceutical industry to promote training in *in vivo* techniques.

John Vane was a towering figure in the physiological tradition of pharmacology. He watched the molecular biology revolution unfold from the sidelines and his confidence in bioassay as an engine for the generation of new ideas and discoveries remained undiminished throughout his life. Though he is gone, his students, his research style, his extensive publications and his institute are a continuing testimony to his enormous influence as a scientist and as a man.

R J Flower
William Harvey Research Institute, St Bartholomew's and the Royal London School of Medicine and Dentistry, London, UK

This article is a shortened version of an obituary which first appeared in pA_2, the Members' magazine of the British Pharmacological Society and is reproduced here with permission.

Members may like to know that over £2,500 has been raised for Cancer BACUP in memory of Rob Clarke who died last August (*Physiology News* 2004, **57**, 49)

Nicholas J Davey

1957 – 2005

The untimely death of Nick Davey, who was tragically killed in a car accident on his way to work in February, is being felt not only by his family, friends and colleagues but also by the many volunteers among the spinal cord injured fraternity who had come to trust and respect Nick's efforts to improve their prospects through his scientific research.

Nick graduated from Bedford College London in 1980 with a BSc in Zoology. He then spent 3 years at Imperial College researching the neural control of breathing, work that led to his PhD and Diploma of Imperial College in 1983. In 1983 he came to work with me in the Department of Physiology at University College. We continued a close collaboration for the ensuing 22 years. That first project revolved around the need to understand more exactly the role of the muscle spindle and its efferent innervation, the gamma motoneurone supply, in the control of movement. While engaged on this work, we spent some time trying to figure out why the discharges of gamma motoneurones became synchronised following acute spinal cord section in animals. This study led directly to Nick's major contributions in scientific research and spinal cord injury. Realising that the finding would have implications for human spinal cord injury if it applied to alpha motoneurones in man, Nick suggested that we expand our research into the clinical field. By coincidence, Nick lived within a few miles of the National Spinal Injuries Centre (NSIC) at Stoke Mandeville Hospital. He approached the staff of the Centre and quickly satisfied them that an electro-physiological examination of the discharge characteristics of motor units in spinal cord injury would be of value in obtaining a better understanding of the impact of such devastating injury on the execution and control of movement and on spasticity. Nick's enthusiasm for his research and his consideration for the well-being of research volunteers soon convinced staff and patients at Stoke Mandeville that the work should be treated seriously. The upshot was that he established a laboratory on site so that volunteers could participate in the research along-side their treatment and physiotherapy. In 1986 he was awarded the position of Honorary Research Physiologist in the NSIC.

In 1988, Nick moved to the Department of Physiology at Charing Cross and Westminster Medical School, based at the Charing Cross Hospital where we continued our research collaboration. Nick's initial appointment as temporary lecturer, then post-doctoral research assistant and Clinical Scientist reflected more the exigencies of the Medical School as it moved towards merger with Imperial College than it did his research achievements. Full recognition of his research standing came with appointment as lecturer in 1995, initially at the Charing Cross and Westminster Medical School and then within Imperial College. He was promoted to Senior Lecturer in the Division of Neuroscience and Psychological Medicine in 2002.

Research in a particular field often receives a boost with the emergence of a new technique. Nick realised the potential of transcranial magnetic stimulation (TMS) of the brain soon after its inception in the mid 1980s. Here was a way to test the integrity of the corticospinal tract, the pathway from brain to muscle that, when damaged in spinal cord injury, results in loss of voluntary control of movement. Over a number of years, Nick's use of TMS led to a detailed understanding of how the surviving connections from brain to muscle adapt to spinal cord injury and how this plasticity of central nervous system function impacts on any residual ability to move. It was a field that intrigued Nick and engaged his research efforts with the expectation that a certain amount of recovery from spinal cord injury might be possible if this plasticity could be manipulated. His most recent research showed that magnetic stimuli repeated at low rates and with a specific pattern can have a therapeutic effect. Clinical assessments and functional tests improved and these were accompanied by physiological changes in the pathway from the motor cortex to motoneurones. Nick was also a key player in the first stage of a Clinical Initiative funded by the International Spinal Research Trust to develop improved physiological tools for the assessment of the level and completeness of spinal cord injury. Nick's finding with repetitive magnetic stimulation is now set to have a major role in the next stage of this Clinical Initiative. Repetitive TMS will be used as a therapy in spinal cord injury against which the efficacy of the physiological tools designed in stage one can be evaluated.

Nick Davey will be remembered by many colleagues and students as the man with the magnet, and quite rightly. For several years he organised a seminar series, the *Magnetic Stimulation Club*, at Charing Cross with national and international speakers. He was a co-editor of a definitive *Handbook of Transcranial Magnetic Stimulation* in 2002 and contributed elsewhere to many book chapters and original journal articles on the technique and its application. Although spinal cord injury came to dominate his research, he made contributions to the understanding of Parkinson's disease, arthritis, chronic fatigue, back pain and schizophrenia. Among his more eclectic

Nick with daughter Tilly

activities with magnetic stimulation was collaboration with a dancer and choreographer that led to an investigation of motor control under weightless conditions above the Bay of Biscay in parabolic flight aboard an Airbus A300!

Nick was recognised as an accomplished teacher as well as a scientist. He was always ready to share his knowledge and many medical and science undergraduate and postgraduate students have benefited from his knowledgeable and enthusiastic instruction. He was likewise conscious of the need for scientists to relate to the public. He organised demonstrations at the Science Museum as part of Brain Awareness Week and appeared on several BBC television programmes concerned with popularising science.

Nick is survived by his wife Cicely and two year old daughter Tilly.

Peter H Ellaway
Department of Movement and Balance, Imperial College School of Medicine, London, UK

Deceased Members

The Society reports, with regret, the death of **G Hugh Begbie** (Edinburgh) since the last issue of the magazine. Hugh was elected as a Member in 1964 and served as a Press Editor for the *Quarterly Journal of Experimental Physiology.*

The Society's journals

The Editorial Boards of *The Journal of Physiology* and *Experimental Physiology* took the opportunity of the IUPS meeting in San Diego in April to hold meetings in the USA. Unsurprisingly, given the venue, a record 41 Editors were present at *The Journal of Physiology* Board meeting, nearly half being our North American Editors. This was Stewart Sage's last meeting as Chair of the Board. During his term of office Stewart restructured the Board to reflect developments in the content of *The Journal*. His role in maintaining *The Journal* as a successful, dynamic publication through a time of upheaval, with a change of publisher to Blackwell Publishing and the reorganisation of the Publications Office, was recognised by Deputy Chair Prem Kumar on behalf of the Board. *Experimental Physiology's* Board meeting was more informal and underlined EP's intention to raise its profile in the US and bring the newly appointed US Deputy Chair, Nanduri Prabhakar, up to date on current strategy.

How have the journals fared during their first year with Blackwell Publishing? In both cases there has been a high rate of subscription renewal and every effort has been made to secure lapsed subscriptions. In addition, the inclusion of both journals in Blackwell's consortial deals has meant that they are now in many more libraries than before. Our marketing manager at Blackwell, Alison Brown, has worked hard to generate interest in the journals, promoting them widely at conferences and meetings. Alison is always pleased to hear about meetings at which it would be appropriate to publicise the journals and can be contacted via the Publications Office (journals@physoc.org). Like everyone else, publishers are interested in the enormous potential of the Chinese market and Blackwell will be opening a Shanghai office. They suggested that the Editorial Boards should consider appointing a Chinese Editor to encourage scientists in the region to publish in our journals.

The 2003 impact factors were down slightly for both journals, which was disappointing and the Boards are taking measures to reverse the decline. One aspect on which both Boards have focused is the time taken to review papers, and times to first report have been reduced for both journals. Both journals also continue to exploit the popularity of themed issues containing invited reviews by acknowledged experts in emerging and dynamic fields. During 2005 *The Journal of Physiology* will publish two themed issues and two issues based on *Journal*-sponsored symposia. All *Experimental Physiology* issues will contain either symposium reports or themed sets of invited papers which reflect the journal's focus on translation and integration. *Experimental Physiology* is also introducing 'Exchange of Views' – 'back-to-back' reviews with commentaries and responses on controversial topics. *The Journal of Physiology* Board has introduced Letters to the Editor on a trial basis and has revised guidelines for Topical Reviews to make them a less onerous proposition for invited authors. Sectionalisation of the JP table of contents continues to be debated and will be fine-tuned to make it as flexible as possible. Continuous monitoring of the acceptance rate has ensured that only the highest quality papers are accepted for publication.

'Open access' publishing, discussed in detail on p. 25 of this issue, has been in the news for the past year as proponents have lobbied for a change in the way journals are published. Blackwell has announced a year-long 'author pays' trial, Online Open, which will allow authors to request immediate open access to their papers on payment of a fee of £1,250/US$2,500. Both Boards agreed that the journals should take part in this, though neither realistically expects much of an uptake until authors can include full publication costs in their grant applications. Grant providers are also influencing the policies of the journals. The National Institutes of Health archiving policy comes into force in May and requests NIH grantees to archive their accepted papers in PubMed Central within 12 months of acceptance. The Wellcome Trust is likely to request that papers produced by their grantees are archived in 'open access' archives within 6 months of publication. Upwards of 40% of papers in *The Journal of Physiology* and 18% of papers in *Experimental Physiology* emanate from labs funded by NIH or Wellcome, so these policies are defining and curtailing the periods when the journals can be sold to subscribers. This poses a particular threat to *Experimental Physiology* and the EP Board have asked Blackwell to investigate the option of publishing more frequently online and less frequently in print. The Society's funds, and hence its activities, depend to a large extent at present on income from publishing. Opinions are divided on how seriously open access will affect societies and publishers, but at the moment it seems that we are likely to see some effect. The shifting landscape of publishing will keep those of us charged with nuturing the Society's publications on our toes.

Carol Huxley
Managing Editor

Science and the General Election

On 1 March the Chairman of our Executive Committee Giovanni Mann, Mike Withnall, Executive Director of the Biosciences Federation, and myself, attended an event organised by Parliament at Portcullis House in the run up to the General Election.

Four speakers were brave enough to present their views on science policy on behalf of their respective parties: Lord Sainsbury of Turville (current Minister for Science and Innovation), Robert Key (Shadow Science Minister), Evan Harris (Liberal Democrat Member of the House of Commons Science and Technology Select Committee) and Simon Thomas (Chief Whip and Frontbench Spokesperson for Plaid Cymru). They addressed a standing room only forum of just about anybody with a stake in the future of science, including academics, journalists, Learned Societies, Research Councils, university research support and technology transfer staff, intermediary organisations and science and technology-based companies. The event was chaired by the President of the Royal Society, Lord May, and the President of the Royal Academy of Engineering, Lord Broers. MPs Andrew Morrison and Brian Iddon hosted.

A lively debate ensued between the various speakers and delegates from the floor. There was cross-party support for tackling climate change, the science and innovation agenda, and the use of animals in research, and also a consensus that Lord Sainsbury had done a sterling job on behalf of science in his years as Science Minister. However, this didn't let the Government off the hook on many hot issues.

The Lib Dems highlighted the crisis in careers in science and in support for science teaching in schools, and criticised Labour plans for increasing student debts. Academia is still plagued by short- term contracts, and career structures in science are still unrepresentative and prejudiced against women and ethnic minorities. The Lib Dems would like to see the reinstatement of student grants and initiatives to tackle the existing student debt mountain. The suggestion was that this might be achieved by increasing taxes for people earning more than £100k per annum. They would also like to address the balance between military and civil R&D, allocating more resources to clinical research, and helping developing countries with new initiatives to help them train and retain their own scientists, addressing their problem of brain drain to the developed world. Although supporting innovation, the Lib Dems were also concerned about the possibility of public money being subverted to subsidise the private sector.

The Conservatives considered the intimidating activities of some animal rights activists to be an absolute scandal. All the parties agreed that this was an issue that needed to be tackled and were broadly supportive of the Government's attempts to tighten up legislation in this area. The Lib Dems were also pro dealing with animal rights activists to help make the UK a good place to conduct valuable research applied to medicine. A delegate from the pharmaceutical industry highlighted the importance of this. The UK is no longer unique in science, and the activities of animal rights activists, together with the increasing burden of regulation and costs of collaborative research, could cause pharmaceutical industry investment in the UK to go into substantial decline. The UK cannot afford to be complacent in its dealings with the pharmaceutical industry – countries like Singapore are already pro-active in providing excellent packages to encourage companies to relocate there.

The RAE also proved to be a hot topic. The Conservatives acknowledged that they had no plans to scrap it, but that its existing criteria are distorting the relationship between teaching and research. The Conservatives propose to address this by creating a new research funding body, modelled on organisations such as the American NSF and NIH, that would be big and powerful enough to resist short term political interferences. The Lib Dems also believed that the RAE distorts the publication and research decision-making process. The focus should be on supporting departmental research quality, not be structured in such a way as to concentrate resources increasingly in an ever smaller pool of elite universities. Lord Sainsbury acknowledged that the RAE is possibly at the end of its life in its present form, and that this would be addressed by a future Labour Government. The concept of dual funding was likely to continue, but alternative less bureaucratic mechanisms for its allocation would be considered, including the possibility of using Research Council funding distributions as the calculator for distributing HEFCE overheads. The spread of regional support would also be tackled.

All the Parties agreed that more needed to be done to encourage young people to study science, including development of a more exciting school science curriculum, and new schemes to help young scientists interact with schools. Concerns were raised about the Government having signed the Bologna Agreement, an EU Agreement concerned with harmonising tertiary education across Europe. The Government promised that it would approach its implementation cautiously. The Conservatives noted that the recent big increase in visa costs for international students was probably a mistake and, unless addressed, was likely to undermine the many worthwhile initiatives to help universities recruit foreign students. Plaid Cymru were naturally focused on Wales' scientific development needs, so they also highlighted the need for a good revamped science curriculum.

What was encouraging was the strength of the cross-Party consensus for supporting science research and science education. Needless to say, this is a priority for the Physiological Society and our sister societies, so we intend to keep lobbying whatever Government comes into power to keep this firmly on the agenda. Long live science!

Liz Bell
Head of External Affairs

New Council Members

To conclude our article on the new ordinary Council members elected at the AGM last autumn, the remaining two biographies are published below. We also include information about Helen Taylor and Patricia de Winter who were elected as Affiliate representatives.

Patrick Harrison has been a Senior Lecturer in the Dept of Physiology, University College Cork, since 2001. Prior to that he was a Lecturer in the Department of Medicine at Glasgow. He got his PhD in Virology from Glasgow in 1992 and then did postdocs in Cambridge, Vienna and Edinburgh. His research interests include use of virus vectors to study physiological systems, especially Parkinson's disease. Patrick has been Director of the Society's Annual Molecular Techniques Workshop since 1996.

Anne King is a Reader in Neuroscience at the School of Biomedical Sciences, University of Leeds. Originally from Edinburgh, she graduated with a BSc in Physiology from Aberdeen University, and then obtained a PhD in Neuroscience from Southampton University. Following an MRC post-doctoral training fellowship in London at St Bartholomew's HMC (with A Nistri) and then a research assistantship at UCL (with C Woolf), interspersed with brief but extremely enjoyable sojourns to the labs of collaborators in Paris (E Cherubini & Y Ben-Ari), Anne took up a lectureship in physiology at Leeds.

Anne's research career began at a time in neuroscience when the use of in vitro brain and spinal cord preparations was on the ascendancy and her work has utilised such approaches to investigate signalling and neuronal communication in spinal cord. The focus of her present research is synaptic modulation of somatosensory processing in the sensory dorsal horn with a particular emphasis on nociception (pain) and analgesia. Anne has yet to be motivated by a mid-life crisis into running a marathon (what's the trick, Ian?) but probably has enough on her plate guiding two teenagers through the maze of the current education system into viable careers!

Biographies of **Clive Orchard**, **Paul Greenhaff**, **Stafford Lightman** and born-again marathon-er **Ian McGrath** were published in *Physiology News,* 2005, **58**, 34. A profile of **James Jones**, who is also a member of the Editorial Board of *The Journal of Physiology*, appeared in *Physiology News* 2004, **57**, 35.

Affiliate Members of Council

Helen Taylor is not a doctor or a professor in anything at this moment in time, but slowly working towards it. She got her passion for physiology as a

BSc student at the University of Sheffield where she stayed on to do a PhD with Louise Robson. She is currently in her 2nd year and at the stage of thinking 'Help! I'm half way through'. Time flies when you are having fun! At present Helen is investigating the function and regulation chloride channels in the kidney nephron.

Patricia de Winter was elected as one of the two Affiliate representatives when she was a PhD student at Birkbeck, University of London. She has since obtained her PhD and now works as a Post Doc in Giovanni Mann's lab at King's College London. Patricia has a somewhat chequered

history and entered science through a non-traditional route. She originally trained as a nurse at the Royal Free Hospital in London and went on to specialise in urology. She moved out of clinical nursing and into research nursing and became the manager of a Clinical Trials and Research Unit at UCL. One day Patricia was sitting having coffee with her then boss Mike Craggs and the words 'I want to be a scientist' spontaneously emerged from her mouth. Patricia recalls that he looked at her in surprise and replied in a serious tone that one doesn't just 'become a scientist … it takes years of hard work'. But the seed was sown and when Patricia completed a part-time MSc in Physiology at Birkbeck, she decided that science was definitely for her. At that time she had Associate Membership of the Society (this membership category is now defunct), but became an Affiliate on enrolling for a PhD. Patricia feels she has benefited greatly from the Society by attending workshops and meetings and therefore decided that she would like to contribute by standing as an Affiliate representative on Council. Since becoming a representative Patricia has attended several Council and subcommittee meetings and co-organised the Seville Young Physiologists' Symposium, which took place in February. As her role is to represent affiliates' views Patricia would very much welcome suggestions and can be contacted at patricia.de_winter@ucl.ac.uk.

Stewart Sage chaired his final meeting of *The Journal of Physiology* Editorial Board in San Diego in March (see full report on p. 46).

Stewart, pictured left at the Editors' supper in Del Mar, took on the role in 2002. Chair-Elect William Large (right) takes over on 1 July.

Wanted: dedicated or alive

You used to know where you were with advertisements for academic jobs.

'The Physiology department of the University of Poppingham requires a lecturer. Duties will be teaching, supervision of graduate students, and conducting research.'

Of course, these adverts often concealed a whole raft of hidden agendas, and more often than not some research areas would be 'preferred', but at least the language in the advertisement was to the point.

Not any more.

Nowadays most academic job advertisements in the UK give the impression of having been written by a committee consisting of a Head of Department with messianic delusions, one or more human resources 'professionals' (the inverted commas are mine), and a public relations flack in the grip of a Prozac frenzy. And all of them seem to have been on some special course in mangling English.

Yes, these adverts now have a language all of their own. The odd thing, though, is that they are all so similar – despite the hyperbole and obscurantist language – that they could practically have been written by a computer programme.

The simplest change is the proliferation of superfluous adjectives, or, to be more precise, Obligatory Adjectival Qualifiers (OAQs for short). An OAQ is an adjective that must automatically precede a noun every time that particular noun appears. Some examples:

'world-class' (institution, or research)

'outstanding' (individual)
[also 'exceptional', 'pro-active', 'committed', 'energetic']

'exciting' (opportunity)

'state-of-the-art' (facilities, buildings)

'leading' (centre) [also 'world-leading']

'proven' (ability)

Then there are the phrases that have both a literal and a shorthand, or parallel, meaning. Examples:

The institution:

'An exciting, vibrant, research-led academic community': Russell group.

'Progressive and innovative' (also 'modern and innovative'): ex-Poly.

'High-quality student-centred learning environment': We have a new building and are desperately trying to enrol enough students to fill it.

'Committed to anticipating and satisfying students', employers' and clients' needs': Staff will work for food.

'One of the countries most popular student destinations': Nothing stands out about the University but thank heaven the night-life and the cheap booze still brings in the punters.

'Offering opportunities to work with leading international academics whose visions are shaping tomorrow's world': I don't think they've got my antidepressant dose quite right at the moment.

You:

'A committed and work-focused individual': Prepared to work 50+ hrs a week for little money on a fixed-term contract.

'A high-calibre and driven individual': You should be unashamed or at least unaware of your Borderline Personality Disorder.

The job and department:

'We are committed to personal development': We have a widely-loathed staff appraisal scheme.

'An innovative, challenging work environment': You might get a desk.

'We have pursued a focused strategy of appointing world-class researchers': In: Professors with Programme grants; Out: Teaching staff over 50.

'Staff are integrated into cross-cutting, multi-disciplinary themes': Our senior managers believe strongly in putting their oar in.

'We aim for the highest levels of research excellence': Five-star this time, or early retirements all round.

I should say that all the above examples are real: you couldn't make this stuff up. And this is only a starter pack. When you come across more examples – and believe me, you will – how about sending them in?

Finally, to end on a positive note (sort of) – the observant among you will have noticed that, should you ever need to, you can now write your own advert simply by selecting the appropriate phrases from the lists above.

Enjoy.

Mark Cain

Neuroglia

Edited by Helmut Kettenmann and Bruce R Ransom. 2004, Oxford University Press. 601 pp, £85.00
ISBN 0-19-515222-0

The rate of progress in the field of neuroglia research can be readily appreciated by considering the following. The first paper published by one of the editors of this book (BRR) in 1973 was titled *Ionic determinants of membrane potential of cells presumed to be glia in cerebral cortex of cat*. This title provides a snapshot of the relative importance placed on neuroglial cells only 30 years ago. First, neuroglial cells were classified as a single entity (as the techniques of the day were incapable of reliably distinguishing between different neuroglial cell types) and, second, neuroglial cells were classified by what they could not do (generate action potentials) rather than by their own specific properties. This neurone-centric viewpoint is perhaps understandable, particularly from an electrophysiological viewpoint. Who can forget the visceral thrill of impaling ones first neurone and watching the resulting pattern of action potentials in response to current injection on a storage scope? The more passive response of the neuroglial cell simply does not pack the same punch. However, after reading this book the reader will be acutely aware that generating action potentials is one of the few functions that neuroglial cells are incapable of, although, as described in Chapter 9, astrocytes do contain both I_{Na} and I_K, as well as a host of other voltage gated ion channels, but at densities inconsistent with action potential generation.

This second edition of *Neuroglia* has been tightened up considerably, with 47 chapters contained within 601 pages, compared to the first volume (published in 1995), which contained 69 chapters in 1,079 pages. This condensation of information is one of the book's greatest strengths as most chapters are about 10 pages long and information is easy to find. The book is divided into three main sections preceded by an initial historical perspectives chapter: (i) properties of neuroglial cells, comprising 17 chapters devoted to morphology, lineage, and physiological and biochemical properties of neuroglial cells; (ii) functions of neuroglial cells, comprising 14 chapters, concerning myelin, development, immune function, formation of the blood brain barrier, and influence on neurones; and (iii) disease and neuroglial cells, comprising 15 chapters, which deal with glial injury and recovery of function, multiple sclerosis, ischaemic damage and other pathological conditions.

The first chapter is an historical perspective of 'who did what and when', which apportions appropriate credit to initial discoveries and descriptions of neuroglial cells. This may sound rather dry but I found it the most readable chapter of the book. If you think Virchow was the first to identify neuroglial cells, read on. He did coin the word glia but his description of glia was mainly conceptual rather than definitive descriptions of individual cell morphology. This unique chapter was facilitated by the collection of original books and manuscripts in German by key participants in the infancy of neuroglia research in the possession of one of the editors (HK). The first section concerns properties of neuroglia and describes all the basic properties of each type of neuroglial cell. This may sound dull, but the enthusiasm of the respective authors of each chapter has brought the topics to life and it makes for edifying reading. As one who has studied neuroglial cells for almost 10 years I was surprised at the nuggets of information that kept popping up. The second section concerning the function of neuroglial cells is fascinating in describing their diverse properties. What comes across clearly in these chapters is the communication between neurones and neuroglia. Whichever function neurones perform, it appears that neuroglial cells are intimately involved either in facilitating that particular function, or in rapidly restoring homeostasis in order for neurones to continue functioning. Considering how important neuroglial cells are to normal brain function, it stands to reason that when neuroglial cells malfunction the resulting pathology will be correspondingly devastating and this is the subject of the third section. The most widely recognised example of neuroglial cell malfunction resulting in pathology is multiple sclerosis, which has long been recognised as an oligodendrocyte/myelin malfunction that affects neural elements (axon conduction). The role of neuroglial cells in neoplasia is key, as brain tumours are all of glial origin; unlike peripheral cancers, which can metastasise to the brain, brain tumours never invade the periphery. This topic is obviously of most interest from the clinical viewpoint, and the basic groundwork described in the first two sections will surely lead to increased knowledge and hopefully therapeutic strategies to deal with neuroglia-associated pathologies.

The recent considerable progress in the field of neuroglia research is in large part due to the considerable efforts of both editors of this book (who also co-founded the journal *Glia*), whose lifelong devotion to the topic has produced, either via collaboration, training or conversion of previously cynical colleagues, a growing devoted army of tireless campaigners whose desire is to see the neuroglial cell rightly elevated to the same status as neurones. After reading this book the reader will surely agree that this is nothing less than these fascinating and diverse cells deserve.

Angus Brown

Other books received. Reviews may be carried in future issues of *Physiology News*.

Innovation in pain management. Wellcome Witnesses to Twentieth Century Medicine, Vol 21. Edited by L A Reynolds and E M Tansey.

The fatal inheritance. John Bligh.

Myosin, muscle and motility. Edited by Ken Holmes, Bob Simmons and David Trentham.

ESBRA 2005

Canterbury, UK
4-7 September 2005

ESBRA 2005 (Conference of the European Society for Biomedical Research on Alcoholism) is being held in Canterbury from 4-7 September. Registration details can be found at http://www.esbra2005.org

PHARMACOGENOMICS

Wellcome Trust Genome Campus, Hinxton, Cambridge, UK
14-18 September 2005

Cold Spring Harbor/Wellcome Trust conference focusing on the opportunities presented by the growing contribution of emerging genomic information and technologies to interdisciplinary approaches in the study of variable responses of humans to drugs and toxic agents, and how research may benefit the individual.
http://www.meetings.cshl.edu

FUNCTIONAL GENOMICS OF MAMMALIAN NERVOUS SYSTEMS

Wellcome Trust Genome Campus, Hinxton, Cambridge, UK
28 September-2 October 2005

This first Cold Spring Harbor Laboratory/Wellcome trust conference will address approaches ranging from molecular biology to behaving animal studies, from single gene to complex sets of genes, from synapses to networked brain functions. Closing date for registration and abstracts 6 July.
http://www.meetings.cshl.edu

BIOSCIENCES FEDERATION EDUCATION COLLOQUIUM

Carisbrooke Hall, Marble Arch, London
12 October 2005

A 1 day workshop bringing together school and university teachers, employers and other educational professionals to discuss the balance between developing skills and acquiring knowledge. The main focus will be what makes a graduate employable and how this is being addressed through education. Free registration.
http://www.bsf.ac.uk/edu

EUROPEAN COUNCIL FOR CARDIOVASCULAR RESEARCH

La Colle sur Loup, Nice, France
14-16 October 2005

The 10th Annual Meeting of ECCR will include keynote speakers, oral and poster presentations, workshops and hot topic sessions.
Full details available at www.eccr.org

BIOSCIENCES FEDERATION CAREERS CONFERENCES

Bristol University - 5 November
Westminster University - 19 November
Newcastle University - 3 December

All day careers conferences during 2005 are being held in November/December for life science undergraduates (graduating in 2006 or 2007) and postgraduate students. (If you have recently graduated or are a postdoc you are also more than welcome to attend). Each conference includes a range of talks on career choices and further training and an exhibition.

THE JOURNAL OF PHYSIOLOGY SYMPOSIUM

Placenta/Endocrine mechanisms of programming at the 3rd International Congress on the Developmental Origins of Health and Disease, Toronto, Canada
16-20 November 2005

Full details in the next issue of the magazine or at http://jp.physoc.org

FASEB 2006

Moscone Convention Center, San Francisco, CA, USA
1-5 April 2006

http:www.faseb.org/meetings/eb2006

FAOPS 2006

Federation of Asian and Oceanian Physiological Societies, Seoul, Korea
15-18 October 2006

http://www.faops2006.org

FEDERATION OF EUROPEAN NEUROSCIENCE SOCIETIES

Forum of European Neuroscience in Vienna, Austria
8-12 July 2006

http://www.fens.org

Noticeboard

Notices for the Autumn 2005 issue of *Physiology News* should reach the Publications Office by 9 June. Please send contributions to lrimmer@physoc.org.

Please note that whilst Members are welcome to advertise relevant events in *Physiology News* and on the Society's website, advertisements via email will be restricted to events sponsored by the Physiological Society.

The Physiological Society Meetings 2005/2006

University of Bristol
20-23 July (Wed-Sat)
International Joint Meeting of the Physiological Society and FEPS

University of Oxford
5-7 September (Mon-Wed)
Ion channels, genes and regulation in smooth muscle

For further details please visit the Society's website
http://www.physoc.org

IUPS 2009

Kyoto, Japan
27 July-1 August 2009

http://www.iups.org

IUPS 2013

Birmingham, UK
July

http://www.iups.org
http://www.physoc.org

Where does your future lie?

Life Science Careers 2005

Organised by:

BIOSCIENCES FEDERATION

Details of each event and booking forms are available from:

www.bsf.ac.uk/careers.htm

Are you a life science undergraduate or postgraduate student?

Do you want to learn about career opportunities in life science today?

If so, don't miss out on the Life Science Careers Conferences:

5	**November**	**Bristol**
19	**November**	**Westminster, London**
3	**December**	**Newcastle**

Programme includes:

- Talks on R&D, science communication, postgraduate/postdoctoral opportunities, teaching, patent examination, careers in plant sciences and much more.....
- CVs and job applications
- CV checking service

NewScientist

The Physiological Society

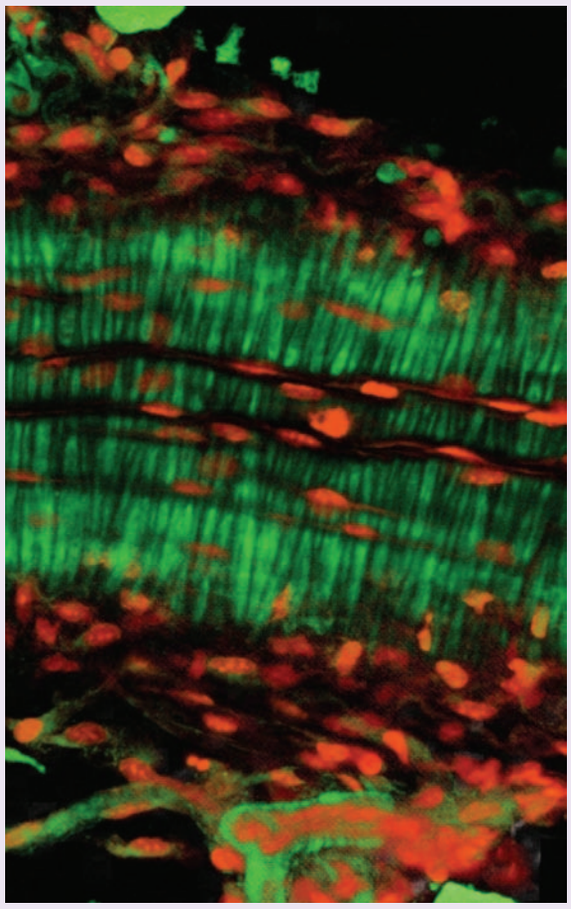
The Biochemical Society Founded 1911

gsk GlaxoSmithKline

British Pharmacological Society

AstraZeneca

society for general Microbiology



The confocal image shows a mouse mesenteric artery stained with a nuclear dye (SYTO $62^{\pm 1}$ μg/ml, red) and a fluorescent α_1-adrenoceptor ligand (QAPB 0.1 μM, green). All smooth muscle cells stain positive for QAPB and thus contain α_1-adrenoceptors. A population of cells in the adventitia also expresses α_1-adrenoceptors. The endothelial cells (identified by their nuclei) can be see running through the center of the vessel and appear to be aligned with the folds in the internal elastic lamina of this un-pressurised vessel. The adventitia is densely populated with cells (red nuclei). Adventitial nerve fibers travelling parallel to the vessel are also visible. The unusual looking structure at the bottom of the image is a small arteriole which appears to express high levels of α_1-adrenoceptors.

Taken from a presentation by Ian McGrath at the Physiological Society sponsored symposium *New aspects of artery resistance and structure* in Seville, Spain. A report of the symposium appears on p. 7 of this issue and papers from the symposium will be published in the July issue of *Experimental Physiology*.