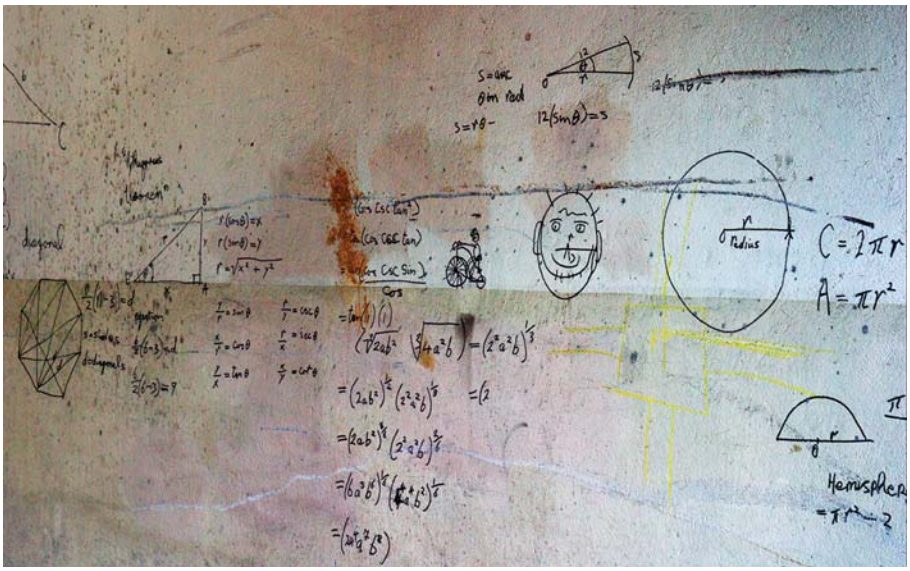
PHYSIOLOGYNEWS

winter 2004 | number 57

King's College London Meeting
Seville, Spain Meeting
Images of Cork and Newcastle

Also featuring:
My 10 key papers *New Series*
A week in the life of ...
Doping – a misuse of science
Keeping warm in cold sea water
Understanding standing
How the Society works

A publication of the Physiological Society

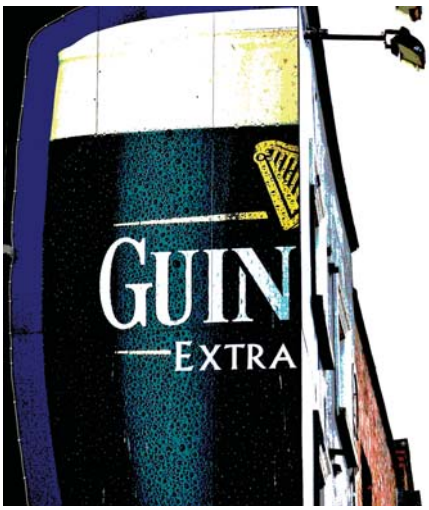


More images from the Meeting appear on the inside back cover

Images of Cork

A pictorial record of the city hosting the Physiological Society Meeting and AGM from 1-3 September, 2004

(photos by 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 photo

Cover illustration from Duchamp *et al.* Mitochondrial proton conductance in cold adapted king penguins, p ...

(photograph by Philippe Bruniaux)

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Grant schemes have changed. For full information on Members' and Affiliates' Grants, Pfizer *in vivo* Physiology Grants, Intercalated BSc Bursaries, Network Interaction Grants, Non-Society Symposia Grants, Postgraduate Support Fund information and the Vacation Studentship Scheme please 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 Spring 2005 issue, No. 58, should reach the Publications Office (lrimmer@physoc.org) by ... January, 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 2004* at http://www.physoc.org)

In this issue

Welcome to the Winter 2004 *Physiology News*.

Austin Elliott

Welcome to King's College London

The Society returns to Guy's Campus for a joint meeting with the Chilean Physiological Society

We are pleased to welcome you back to King's College London for the second meeting of the Physiological Society at our Guy's campus. The first meeting was in December 2000 and had over 900 delegates. This meeting is a joint meeting with the Chilean Physiological Society and we would particularly like to welcome our colleagues from South America who are attending the meeting. Again we believe that we have an exciting programme of symposia, workshops and special lectures, as well as a myriad of communications and posters.

The Academic Department of Physiology is one of five departments making up the School of Biomedical Sciences. The department plays a major role in the teaching of physiology to over 2000 students. Each academic member of the school belongs to one of the five academic departments and almost all are members of one of the College's interdisciplinary research divisions. Research is organised through these divisions where staff are physically located together regardless of their teaching discipline. This has allowed the School and College to develop a number of interdisciplinary research divisions of potential research excellence. Physiology is represented in a number of the research divisions.

The department has 28 members of academic staff. (11 professors, 2 readers, 9 senior lecturers and 6 lecturers).

However, there is an almost equal number of Members of the Physiological Society who are members of other departments (eg Pharmacology and Anatomy) or Schools of King's College (eg Medicine, Dentistry, Health and Life, and the Institute of Psychiatry).

The College research divisions in which physiologists are represented, listed with their Directors, are Cardiovascular (Ajay Shah), Reproductive Health, Endocrinology and Development (Lucilla Poston), Wolfson Centre for Age-Related Diseases (Pat Doherty), Applied Biomedical Sciences (Di Newham), Randall Division of Cell and Molecular Biophysics (Malcolm Irving, FRS), MRC Centre for Developmental Neurobiology (Andrew Lumsden, FRS) and Asthma, Allergy and Lung Biology (Tak Lee).

The Centre of Neuroscience Research has merged with the Wolfson Centre for Age Related Diseases (CARD) to form the 'new' Wolfson CARD, specialising in basic neuroscience, disorders of the CNS, treatment and repair. It will be housed in the new Wolfson Wing (official opening November 2004) and the Hodgkin Building.

The research activities of King's College 'physiologists' are varied and diverse and a few examples of the current research being carried out at King's by the Society's Members are listed on opposite.

We hope you enjoy visiting our campus at Guy's and we all look forward to seeing as many of you as possible at both the scientific and social events.

Roger Linden
Academic Department of Physiology

Above: Mr Thomas Guy (top); the colonade of Guy's Hospital (centre); Jeremy Ward, Lynne Baxter, Bonnie Teague, Katharina Mahn, Phil Aaronson, Silke Becher, Gavin Thomas, Vladimir Snetkov and Greg Knock (bottom).
Below: King's Physiological Society Members gather round a 'modern piece of equipment'

Research activities at KCL

Jeremy Ward (the Society Treasurer) and **Phil Aaronson** lead a team investigating the control of the pulmonary circulation, in particular mechanisms underlying hypoxic pulmonary vasoconstriction; areas of interest include oxygen sensing, calcium sensitization pathways, TRP channels, and the role of the endothelium

The research groups of **Richard Siow** and **Giovanni Mann** (Chair of the Society's Executive Committee) are collaborating in a study of the effects of reactive oxygen species on signal transduction in cultured vascular endothelial and smooth muscle cells, with particular emphasis on the role of transcription factors involved in transactivation of antioxidant stress genes.

Kalwant Authi is attempting to understand the major Ca^{2+} signalling mechanisms in human platelets. He hopes that this will lead to the development of novel therapeutic targets.

Ajay Shah's current research interests are in the mechanisms and pathophysiological roles of reactive oxygen species generation by NADPH oxidases, focussing on cardiac hypertrophy, heart failure, and endothelial dysfunction.

Richard Naftalin's interests relate to glucose transport and to coupling of ion and water transport in epithelia.

Jon Kentish leads a group investigating inotropic mechanisms in healthy and diseased hearts. Using skinned single cardiac myocytes, they are examining the extent to which the dysfunction in the contractile properties of the diseased myocardium can be explained by changes in the protein isoform composition of the myofibrils.

Paul Fraser is working on the signal transduction mechanisms that are responsible for the regulation of capillary permeability in the brain and the retina, and is currently examining how the sensitivity to inflammatory mediators is increased by NADPH oxidase activation.

Ron Jacob is working on calcium regulation and reactive oxygen species in endothelial and vascular smooth muscle cells, with particular interest in perturbations of these mechanisms in pre-eclampsia.

Mike Shattock's group is focusing on how the expression, structure, activity, and location of key ion translocating proteins (channels, pumps and exchangers) in subcellular as well as sarcolemmal membranes may influence the outcome of ischaemia, reperfusion and hypertrophy.

Lucilla Poston's group focuses on two principal areas of research- causes of 'low birthweight' and 'developmental programming of adulthood disease'. Their principal aim is take research from the bench to the bedside.

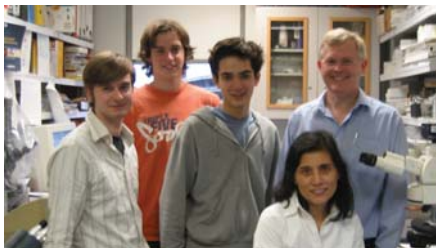
Peter Jones and **Shanta Persaud** are investigating the development of human beta cells; nutritional influences on beta cells during development; signal recognition and transduction in beta cells; the autoimmune process in Type I diabetes; and generating insulin-secreting cells from stem cell populations for transplantation therapy.

David Sugden is currently exploring the role of a novel opsin-like protein (melanopsin), thought to be the light detector responsible for daily photic entrainment of the body's circadian clock in the hypothalamus, and investigating the physiology and pharmacology of melatonin, a major hormonal clock output.

Kevin O'Byrne leads a group investigating the neural mechanisms mediating stress-induced suppression of the hypothalamic gonadotrophin releasing hormone (GnRH) pulse generator, the central regulator of the reproductive axis.

There is a strong group working on CNS barriers, blood-brain barrier and choroid plexus (**Joan Abbott, David Begley, Jane Preston, Sarah Thomas, Malcolm Segal**), both basic physiology and pharmacology (especially transporters, receptors), and applied aspects (CNS drug delivery, clinical relevance). David Begley is currently on a sabbatical from teaching as a GlaxoSmithKline Sabbatical Research Fellow and Sarah Thomas has recently been awarded a Wellcome Trust University Award

Ken Smith's group examines the pathophysiology of axons affected by inflammation and/or demyelination, with a particular interest in the effects of nitric oxide.



From the top:
1 Fetal programme team (Paul Taylor, Natalia Igosheva, Lucilla Poston and James Armitage); 2 Blood-brain barrier team (Joan Abbott, Diana Dolman, Zeeshan Qaiser and David Begley); 3 James Bowe, James Kinsey-Jones, David Bedi, Kevin O'Byrne and Xiao Feng Li; 4 Giovanni Mann, Ling Gao, Alan Watson, Nik Mustafa, Sarah Howatt, Richard Siow, Iram Afzal, Anila Anwar, Iya Goubareva and Sheeja Joy; 5 Nnaemeka Amobi and Christopher Smith; 6 Masayuki Mukaida, Roger Berry, Juelin Deng, Linda McLachie, Max Baghai, Mike Shattock, Philip Eaton, Robert Bell, James Bell, Jason Jennings and Will Fuller

Tom Sears has been working on the projection of tactile and pain afferents from the teeth and gums to the cerebellum and is hoping to investigate the effects of periodontal inflammation on afferent transmission to the cerebellum.

Isabella Gavazzi's research aims at elucidating the role of Eph receptor tyrosine kinases and their ligands, the ephrins, in chronic pain and in failure of regeneration in the injured central nervous system.

The major focus of work in **David Tonge's** laboratory is identification of genes required for regeneration in the nervous system since these might be therapeutically useful in promoting recovery following lesions of the nervous system or loss of neurons during ageing or disease.

Steve McMahon directs the London Pain Consortium. A large part of his research aims at understanding the neuronal mechanisms of chronic pain. Some of the most intractable pain states are associated with damage to the nervous system itself. A second major focus of his laboratory is to develop methods to promote repair of such damage.

Reggie Docherty's group is interested in ion channel expression and function in sensory neurones in general but focuses on two ion channels in particular, NaV1.8 and TRPV1.

Di Newham's interests include: Human skeletal muscle; function, fatigue and control health and disease, rehabilitation interventions and their outcome in disorders affecting the musculo-skeletal and neurological systems, ageing and falls and motion analysis

Nnaemeka Amobi and **Christopher Smith** continue their studies on the basic physiology and pharmacology of human vas deferens - and give their thanks to all of you who have had vasectomies. Their aim is to understand how the contractile properties of the circular and longitudinal muscle contribute to the propulsive function that ensures efficient sperm transport and emission.

Heather Holder-Powell's interests are in the long-term rehabilitation of musculo-skeletal injuries and efficacy of physiotherapy. Current studies are investigating anterior cruciate ligament injuries, anterior knee pain and hamstring injuries.

Roger Linden is studying the brain stem reflexes of mastication and salivation in humans and with Nic Hodson is currently studying the interactions of basic gustatory stimuli on parotid salivary secretion.

Anthea Rowlerson is currently examining the expression of growth regulators (myostatin and the IGF system), and their effects on muscle growth mechanisms in farmed fish (principally seabream) and is carrying out a project designed to identify phenotypic characteristics of human masseter muscle related to craniofacial discrepancies causing malocclusions.

Malcolm Irving's group is focused on molecular mechanisms in muscle contraction and its regulation. They use X-ray and fluorescence methods to measure conformational changes of myosin and troponin in their native environment in isolated muscle cells. Their aim is to describe some fundamental muscle functions at the molecular level by combining information from in vitro and in situ studies.

Gerrard Rafferty's group are interested in the performance of the respiratory and musculoskeletal systems in both health and disease, particularly the interaction of respiratory drive, the load on the respiratory system (lung and chest wall function) and the capacity of the system (respiratory muscles).

Frank Kelly is Director of the Environmental Research Group. They undertake research directed towards understanding the mechanisms by which air pollution impacts on human respiratory health. The Environmental Research Group is a leading provider of air quality and research information in the UK. It manages air quality networks on behalf of DEFRA and local authorities throughout SE England, providing services such as site management, quality assurance, local site operator support and reporting including the dissemination of measurements via the Internet.

Spanish Society of Physiological Sciences (SECF)

The Physiological Society (UK and Eire) and the Dutch Society of Physiology sponsor and participate in the XXXIII SECF Congress to be held in Seville, Spain from 10-13 February, 2005. This will be the third time that the Physiological Society shares meetings with the Spanish Physiological Society and the first for the Dutch Society of Physiology. We hope it will not be the last!

The beauty and charm of Seville need no further praise – use the occasion to enjoy them. It is enough to say that Seville lives up to the expectations of the fans of Beaumarchais, Bizet, Byron, Merimée, Mozart, Pushkin and Rossini, to name a few (only two of which actually knew Seville at first hand!).

We will do our best to make your visit pleasant and the weather usually joins in. In February, our average temperature is 18ºC in the afternoon and 7º before daybreak (but we promise not to start very early). The countryside is green, thanks to an average rain of 52 m^2 in the month; the average humidity is 74%. The average number of days with snow, frost or storm is 0; the average number of rainy days is six, and the sun shines, on average, 5-8 hours per day.

On the Congress

On the afternoon of Thursday, 10 February the Congress will start formally with the Opening Lecture at the Engineering School of the University of Seville (on the grounds of the 1992 World Expo, see plan below) and the Opening Reception at the Reales Alcázares (the Royal Palace). During the following three days the Congress will meet in various rooms of the Engineering School. Members of the Local Organizing Committee will be available to provide orientation and help with audio-visual devices and other practical issues.

Five plenary lecturers will be given by well known scientists, including Bert Sakmann (Nobel Prize in Physiology and Medicine in 1991) and Peter Agre (Nobel Prize in Chemistry 2003). Nine symposia have been organised, intended to cover all areas of physiology and focus on attractive subjects not dealt with at recent meetings.

At the opening reception we will have a guided tour to the Reales Alcazares, a sequence of Palaces dating from the 10th Century. Participants will have the unique opportunity to travel in time as they pass through the different rooms of the Alcazar - from an early Moorish domination to the Christian take-over in the 13th Century. Personalities such as Al-Mutamid or King Don Pedro are emblematic characters strongly linked to Seville, independently of their different ethnic origin.

Seville is an enjoyable place at night. Neighbourhoods like Triana, Arenal, Sierpes, Viapol all offer a number of restaurants, bars and other entertainments places for the visitor. We are preparing a tapas tour around the city, so the visitor can enjoy at very affordable prices the most typical Spanish tapas. The Gala Dinner will take place in Cortijo (Andalusian Farm) in which we will have a Flamenco show. Also available is a special programme of excursions to Carmona, Jerez, Cordoba or Granada for accompanying persons.

M Jose Peral, Ana Ilundain, Luisa Calonge, Mercedes Cano and Pablo Garcia-Miranda

Physiology in Seville

Diego Mir and Raimundo Goberna, of the Departments of Physiology and Biochemistry of the Medical Faculty, organised the XIV SECF Meeting in Seville in 1973. Physiology in Seville has changed substantially since then - four University departments now teach physiology. One is at Universidad Pablo de Olavide (founded a few years ago) and the other three at the Faculties of Biology, Medicine and Pharmacy of the Universidad de Sevilla. The Universidad de Sevilla was founded in 1505 to teach philosophy, law, arts and medicine; biology was added in 1964 and pharmacy in 1970.

The Congress is hosted by the Physiology Departments of the Universidad de Sevilla (http://www.us.es/dfba and http://www.us.es/dfmb/dpto). Seven full professors, 25 lecturers and seven associate professors teach cell, animal and human physiology, among other topics, to several hundred students in each of the three faculties and are also actively involved in graduate teaching and in research.

Work in Ana Ilundain's lab focuses on epithelial transport and cell regulation. Guillermo Alvarez de Toledo leads a group investigating the cellular and molecular mechanisms of neurotransmitter release using electrophysiological and imaging techniques. Lucia Tabares' lab investigates the pathogenic mechanisms participating on the functional deterioration of motor neurons in mouse models.

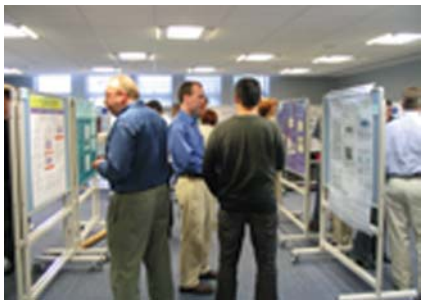
Ana Ilundain
University of Seville, Spain

Newcastle Meeting

Epithelial-bacterial pathogen interactions in Newcastle: microbiologists talking with physiologists

The Physiological Society Focused Meeting on *Epithelial-Bacterial Pathogen Interactions* held on 22-23 July, 2004 at the Research Beehive, University of Newcastle-upon-Tyne, looked at pathogen interactions with respiratory and gut epithelia.

Above: Mike Gray asks a searching question on Florian Lang's presentation
Below: Interest at the poster session.



The Meeting highlighted recent advances in the understanding of the extent to which bacteria and epithelial cells communicate with each other during their interactions at a molecular, cellular and whole tissue levels. This provided an opportunity for cell physiologists and microbiologists at this emerging interface to present their views of how both epithelia and bacteria react once contact has been made. A summary of some of the key scientific issues raised during the meeting is being prepared for publication in *Molecular Microbiology* (PD Aldridge, MA Gray, BH Hirst, CMA Khan. Who's talking to who? Epithelial-bacterial pathogen interactions).

The Meeting benefited from the facilities of the Research Beehive, a newly opened meetings and catering complex at Newcastle University. Speakers soon adapted to the unique experience of presenting to an audience in the round (convex actually), standing between two screens, neither of which were readily visible from the central lectern! Catering was provided by the Courtyard, immediately below the lecture room, the venue for the dinner.

The scientific sessions were a mix of symposia lectures and free communications, with separate poster sessions. *Trends in Microbiology* generously sponsored two prizes, one for an oral communication and the other for a poster, each consisting of cash and a free subscription to any one of the *Trends* journals. Two separate panels selected from the international symposia speakers provided expert adjudication. Myrtani Pieri (University of Oxford) was awarded the oral communication prize for her presentation *Studies on the proton coupling mechanism of the rabbit epithelial H+/peptide transporter PepT1, expressed in Xenopus oocytes* (M Pieri, CAR Boyd and D Meredith). The poster prize was awarded to Pauline M van Diemen (Institute for Animal Health, Compton) for her studies on *Identification of enterohaemorrhagic Escherichia coli genes required for colonisation of the bovine intestine* (PM van Diemen, F Dziva, MP Stevens and TS Wallis).

This was an exciting meeting at the interface of two 'classical' disciplines and as such benefited from the participation of representatives from the two scientific communities. There was much new to learn for everyone. While the scientific programme was organised by *microbiologists* (Phil Aldridge and Anjam Khan) and *physiologists* (Mike Gray and Barry Hirst), our task was made very easy because of the efforts of Gwen Averley (Research Co-ordinator in the Institute for Cell & Molecular Biosciences at the University of Newcastle) who, together with

Symposia speakers

New insights into host response to acute and chronic lung infections. Who is talking to who?

Brad Britigan (University of Cincinnati and The Veterans Administration Medical Center, Cincinnati)
Alterations in airway epithelial cell function by Pseudomonas secretory products

Gerd Doering (University of Tübingen)
Interaction of Pseudomonas aeruginosa and Staphylococcus aureus with the lung epithelium in patients with cystic fibrosis

Ed Galyov (Institute for Animal Health, Compton)
Exploitation of host cells by Burkholderia pseudomallei

Peter Greenberg *(University of Iowa, Iowa City)*
Quorum sensing in Pseudomonas aeruginosa and epithelial cell defenses

Florian Lang (University of Tübingen)
Regulation of transport, apoptosis and fibrosis during lung infection

Subversion of physiological processes in the gut

Gadi Frankel (Imperial College London)
Enteropathogenic E coli and the host cell - molecular intimacy

Martin Kagnoff (University of California, San Diego)
Intestinal epithelium: signals and sensors for mucosal defense

Brendan Kenny (University of Bristol)
Enteropathogenic E coli interference of epithelial cell function

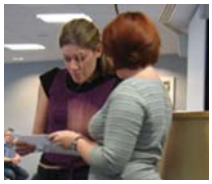
Nicholas Mantis (Children's Hospital and Harvard Medical School)
Secretory IgA: preventing (and promoting) pathogen-epithelial interactions

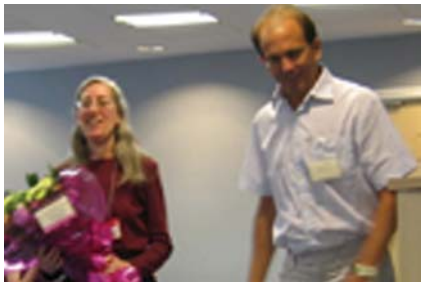
Andre Ouellette (University of California, Irvine)
Paneth cells, α-defensins, and mucosal immunity in the small intestine

Andrea Varro (University of Liverpool)
Dysfunctional signalling from epithelial to mesenchymal cells in Helicobater pylori infection

Emma Chaffin (Meetings Administrator of the Physiological Society) ensured everything ran smoothly. The meeting received additional sponsorship from Novartis. The organisers wish to thank the Physiological Society for sponsoring this Focused Meeting and hence encouraging research at this important interface. Thanks are also due to both the Epithelia and Membrane Transport and GI Tract Special Interest Groups for sponsoring designated lectures by Brad Britigan (University of Cincinnati) and Martin Kagnoff (University of California, San Diego), respectively.

Barry Hirst
Mike Gray
University of Newcastle-upon-Tyne, UK





Clockwise from top left:
Monica Hughes (Head of Institute for Cell & Molecular Biosciences, University of Newcastle), Christopher Edwards (Vice Chancellor, University of Newcastle) and Richard Olver (University of Dundee) in discussion over tea at the Poster session; Myrtani Pieri receiving her prize for the oral communication from Michelle Doherty, *Trends in Microbiology;* Pauline M van Diemen receiving her prize for the poster communication from Michelle Doherty; Mike Gray thanks Gwen Averley for ensuring the smooth running of the Meeting; Barry Hirst, Monica Hughes, Michael Whitaker, Richard Olver, Mike Gray, Gerd Doering, Andrea Varro and Florian Lang enjoying the dinner and discussion; Richard Boyd and David Meredith (Oxford) entertain Dianne Ford and members of her lab from Newcastle at dinner

Bristol Meeting of the Physiological Society and FEPS

The first joint meeting of the Physiological Society and the Federation of European Physiological Societies (FEPS) will be held at the University of Bristol between Wednesday 20 and Saturday 23 July, 2005.

The Meeting promises to be very exciting, including plenary and prize lectures, 14 symposia covering a wide range of physiological topics, a Young Physiologists' symposium and workshops (imaging, stem cell and teaching) and the inaugural Clarke Memorial Symposium. The meeting will be preceded by the 4*th Mammalian Myocardium* symposium (17-20 July) and a Careers' Fair (20 July), and followed by a *Chloride Channels Conference*, to be held between 23 and 24 July.

The historic city of Bristol is well known for its seafaring associations and the engineering achievements of Isambard Kingdom Brunel, as well as for its lively restaurants, clubs and pubs and beautiful Georgian architecture.

The Department of Physiology at the University of Bristol is currently undergoing major changes, with extensive laboratory refurbishment and new research facilities, and recruitment of new staff to increase further its strengths in neuroscience, cell biology and cardiovascular physiology. The Department is looking forward to hosting the joint meeting of the Physiological Society and FEPS and very much looks forward to welcoming you to Bristol in July 2005.

Julian Paton
Clive Orchard
University of Bristol, Bristol, UK

Full details are available at:

http://www.physoc.org/bristol
http://www.bristol.ac.uk/mm2005

A (highly personal) 'Top Ten' of cardiac muscle papers

David Miller launches our new series with a list of publications which he considers as true landmarks in cardiac muscle function

In a foolish moment at the Glasgow Physiological Society Meeting this spring, I accepted Austin Elliott's challenge to list my 'top ten' of papers of cardiac muscle function. I have chosen the historical perspective here. Unlike the new *Dictionary of National Biography*, I have now considered it necessary for the authors to be dead to feature in this list. However, I did thus hope not to offend too many of those I haven't cited. Each of these papers is a true landmark, all frequently referenced (citation counts since 1981 are reported here – Reuter & Seitz (1968) is the 'winner') but perhaps the older ones at least are not so often actually read. With a notional target audience of the interested generalist or, say, a final year undergraduate, I believe each of these papers merits the effort of locating them and reading them in the original. So often cardiac muscle has provided the system in which properties and underlying mechanisms of basic cellular processes could be elucidated, and so it proves for many described here.

1 Ringer's solution – the start of physiological salines

Sydney Ringer made the critical refinements to his eponymous solution in 1883, realising that his technician had previously used London tap water (mM-rich in Ca and K salts) rather than distilled. A solution necessary to sustain a normal heart beat was defined by contraction – the volume change measured by 'Roy's tonometer' – of the cannulated frog ventricle. He assessed beat duration and the steepness of beat onset and decline. With this simple but sensitive bioassay, Ringer convincingly established the required mixture of K, Na and Ca salts of chloride, of near neutral 'acidity' (Sørensen's definition of pH came later in 1909). Hindsight elevates for us the significance of extracellular Ca in cardiac excitation and contraction; extracellular K's role was more prominent for decades because its variation has greater clinical relevance. As with all Ringer's work, we can still learn from reading the original; the power of acute, direct observation to deliver understanding is exemplary.

Ringer, S (1883) A further contribution regarding the influence of the different Constituents of the Blood on the Contraction of the Heart *J. Physiol.* 4, 29-42 (cited >500 times)

2 Starling's law of the heart

Ernest (not 'Frank', as many undergraduates would have us believe) Starling and colleagues elucidated fundamental cardiac function in a series of experiments using a blood–perfused, dog's heart-lung preparation. Starling's insights were empirical, analysing the function of the heart as a pump without any detailed insight into muscle mechanics. He observed that increased atrial filling non-linearly increases cardiac output. It applied to both left and right sides. Atrial filling distends the ventricle in diastole, a more forceful contraction follows and cardiac work increases. In his words 'The law of the heart is therefore … that the mechanical energy set free on passage from the resting to the contracted state depends on the area of "chemically active surfaces", i.e. on the length of the muscle fibres'. Starling's study was significantly preceded by Otto Frank's (1895) which had used frog heart (but see also HG Zimmer (2002), *News Physiol Sci* **17**, 181-184). Indeed, Frank had explicitly brought the insights of Blix and others of the effect of skeletal muscle length on force to bear on cardiac function. The importance for cardiac function remains appropriately

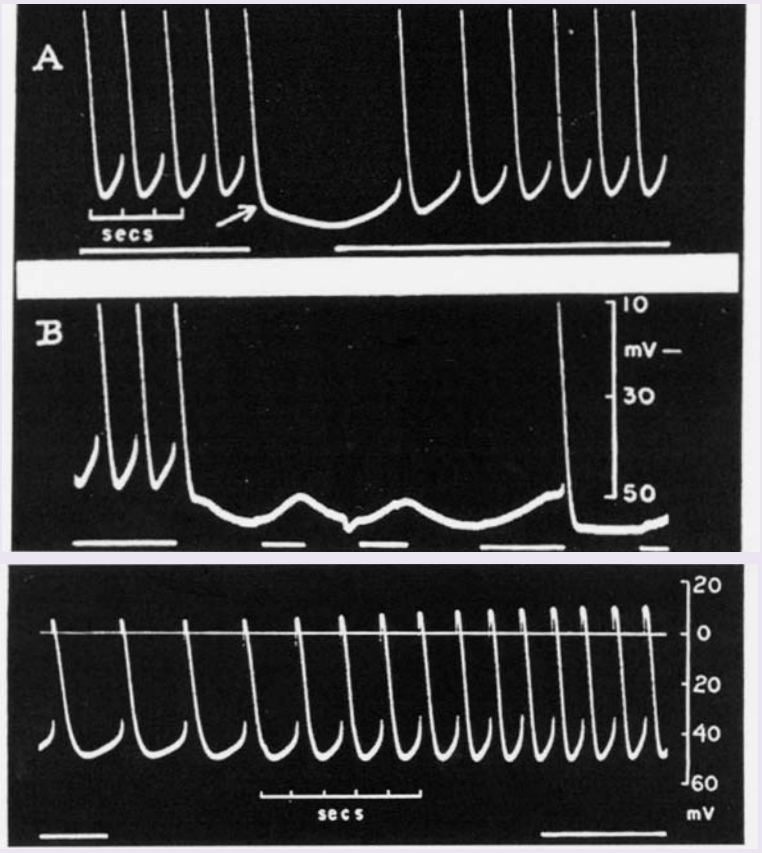


Figure 1. (Figures 4A & B, top, and Figure 10 of Hutter & Trautwein, 1956) Intracellular recording from pacemaker (sinus venosus) cells of frog heart. The upper panels (A and B) show regular, spontaneous action potentials arising from the steadily depolarising 'pacemaker' potential (*NB* directly photographed from the oscilloscope, so the rapid rising phase of each AP does not register). The break in the index line below the traces shows when the vagus nerve was stimulated (at 20Hz), with obvious slowing effects. The bottom trace shows the effect of stimulating the sympathetic nerve (with atropine present to block any effects of inadvertent parasympathetic activity); heart rate rises.

labelled as the ‘Frank-Starling Law of Cardiac Work’.

Patterson SW, Piper H & Starling EH (1914). The regulation of the heart-beat. *J.Physiol* 48, 465-511 (cited >300 times)

3 Silvio Weidmann – the nature of the cardiac action potential

Weidmann’s papers were the first using intracellular recording techniques on cardiac muscle. The familiar form of the box-shaped cardiac AP with its plateau phase emerged with compelling clarity. (Much of Weidmann’s work employed sheep Purkinje fibres). The analysis of cable properties underpinning our understanding of the propagation of excitation through myocardium also flowed from Weidmann’s studies. A crucial finding was that impedance is highest during the plateau – now accounted for in detail by the voltage–dependence and rectifying properties of the ion channels concerned, explaining that total conductance (reflecting ionic fluxes) is lowest during this period of the cardiac cycle.

Weidmann S (1951). Effect of current flow on the membrane potential of cardiac fibres. *J Physiol* 115, 227-236 (cited >390 times)

4 Otto Hutter & Wolfgang Trautwein – cardiac pacemaking and its neural control

The control of the rate of the heartbeat might well epitomise physiology; comprehending this process surely appeals to ‘anyone with a heart’. Hutter and Trautwein’s images of intracellular recordings from frog and tortoise sinus node are true iconic classics (Fig. 1). They show the pacemaker potential, its acceleration by sympathetic nerve stimulation releasing adrenaline (physiological for these species) and slowing under parasympathetic release of acetylcholine. Sympathetic nerve activity increases the slope of the pacemaker potential and lowers the action potential’s threshold. The duration of the individual responses is reduced, as well as their rate being increased. Almost the exact reverse is initiated by acetylcholine (from *vagus* nerve activity). Otto Hutter, in particular, went on the establish the ionic basis for the actions of acetylcholine on K permeability.

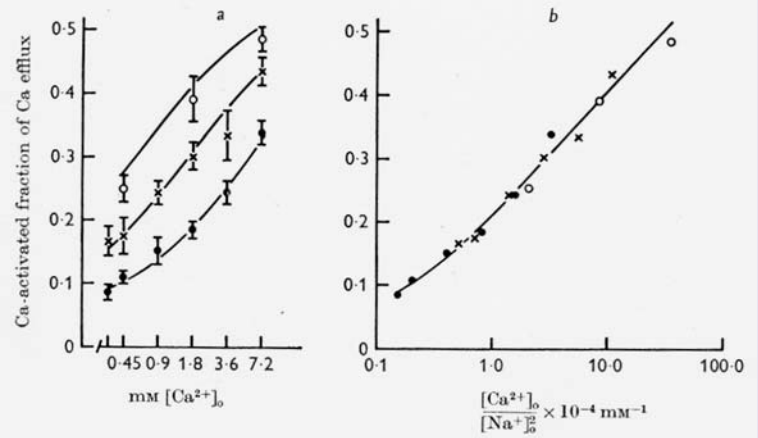


Figure 2. (Fig 7 of Reuter & Seitz, 1968). Ca efflux (as radioactive tracer) from guinea pig atria under different conditions of extracellular [Ca] (abscissa) and [Na] (100% ↓, 50% x, and 25% m of normal). The left panel shows the standard plot, the right re-plots these results with respect to the quotient $[Ca]/[Na]^2$. The results fall on a single line, reflecting the apparent stoichiometry of competition for the Ca-Na exchanger’s binding sites.

Hutter OF & Trautwein W (1956). Vagal and sympathetic effects on the pacemaker fibers in the sinus venosus of the heart. *J.Gen.Physiol.* 39, 715-733 (cited >350 times)

5 Rolf Niedergerke – calcium flux, exchange and compartmentation

Niedergerke’s work occupies a commanding place in muscle physiology, for his earlier work on the role of intracellular Ca and the sliding filament theory alone, but for cardiac muscle in particular. This paper (with others) builds on extensive work using 45Ca radioactive tracer. It clarified that a Ca influx defining cardiac E–C coupling is associated with the action potential and antagonised by extracellular Na. The role of slowly exchanging intracellular stores or compartments was also revealed. (Yes, frog heart has a functional SR). Contemporaneous papers from Glen Langer’s lab confirmed key elements of this story for mammalian myocardium. Ca-Na antagonism is the phenomenological correlate to Ca–Na exchange which, within a few years, was more definitely characterised by Reuter and Seitz.

Niedergerke R (1963). Movements of Ca in beating ventricles of the frog heart. *J.Physiol* 167, 551–580 (cited >390 times)

6 Harald Reuter & Norbert Seitz – the Ca-Na exchanger

Reuter and Seitz made the definitive experiments that explained the Ca-Na antagonism in the contractile behaviour of the heart. Revealing the lack of direct ‘metabolic’ involvement and a low Q_{10} pointed to a non-pump mechanism. A modified ‘Ussing’ exchange diffusion mechanism was proposed with the key characteristics of affinity for Ca and Na at the outer and sarcolemmal surface and for Ca at the inner sarcolemmal surfaces (‘under the conditions tested’ as the authors were careful to qualify) (Fig. 2). Soon afterwards, with Helfried Glitch and Hasso Scholz, Reuter showed the exchanger’s dependence on internal sodium, confirming the reciprocal exchange properties. The high citation rate for this paper is testament to what proved to be a basic membrane transport mechanism subsequently found in many tissues and reflecting every cell’s ‘problem’ of keeping intracellular [Ca] low. Its indirect, but crucial, role in the inotropic action of cardiac glycosides ensured an obvious clinical interest and a new target for therapeutic thinking.

Reuter H & Seitz N (1968). The dependence of calcium efflux from cardiac muscle on temperature and external ion composition. *J.Physiol.*, 195, 451-470 (cited >900 times)

7 George Beeler & Harald Reuter – Ca-current and cardiac contraction

There had been numerous attempts to produce definitive multicellular cardiac voltage clamp studies around this time, but few were as comprehensive and convincing as those reported in this paper. Alarm in the voltage-clamp community followed upon a potentially damning theoretical analysis by Ed Sommer and Ted Johnson (Ann Rev Physiol, 1970, **371**). High ‘quality control’ allowed Beeler and Reuter’s

incisive studies (this is one of three sequential papers) to escape the shadow cast over much of the work by that review. What emerged with clarity was the matching of the voltage dependence of the slow inward (calcium) current and contraction. The time course of restoration of the ability to contract with that of the inactivation recovery of the Ca-current helped to cement the E-C coupling links to the calcium release process described next.

Beeler GW & Reuter H (1970). The relationship between membrane potential, membrane currents and activation of contraction in ventricular myocardial fibres. *J.Physiol.* 207, 210-229 (cited >320 times)

8 Alex Fabiatio – Ca–induced Ca-release (CICR)

In this paper – one of series combining exquisite technological and experimental sophistication – Alex Fabiatio revealed the defining characteristics of CICR, now acknowledged as fundamental to cardiac E-C coupling. It links Ca-entry with the release of Ca from the sarcoplasmic reticulum. Precise conditions - such as $[Mg^{2+}]$, SR loading status *etc* – are critical in defining the behaviour of SR in experiments designed to test CIRC's role. This paper revealed a key aspect; a rise in $[Ca^{2+}]$ must be both large enough and rapid enough in order to trigger release. The characteristics of the putative Ca–release channel were gleaned from Fabiato's painstaking work. CICR is now recognised as a more general cellular mechanism.

Fabiato A (1985). Time and calcium dependence of activation and inactivation of calcium- induced release of calcium from the sarcoplasmic reticulum of a skinned canine cardiac Purkinje cell. *J Gen Physiol* 85: 247-289. (cited >640 times)

9 Mark Hibbert & Brian Jewell – Myofilament Ca-sensitivity increases with sarcomere length (sl)

Myofilament sensitivity to $[Ca^{2+}]$ is not a unique relationship: this paper provided unequivocal evidence that it is length-dependent, augmenting that due to myofilament overlap as revealed in s.l.-tension relationship. (However, a full explanation, rather than description, of the reduced force at s.l.s shorter than the optimum – which is where cardiac cells operate *in vivo* - remains elusive). The Frank-Starling relationship, by then 70 years old, between chamber volume (*i.e.* myocardial length) and contractile strength had gained an additional explanatory mechanism. Hibbert & Jewell's results opened a can of complexity worms that continue to wriggle. It is clear that localised length fluctuations can and do occur dynamically in active cardiac muscle, even under nominally 'isometric' or 'isovolumic' conditions'. Quite how this plays out in terms of length and force and their kinetics for the already complex relationship of these dynamic properties to the Ca transient remains to be clarified.

Hibberd MG & Jewell BR (1982). Calcium- and length-dependent force production in rat ventricular muscle. *J Physiol*. 329: 527-540 (cited >200 times)

10 Hepeng Cheng, Jon Lederer and Mark Cannell – calcium sparks

This paper laid the practical foundations for the current cardiac E-C coupling paradigm of discrete, localised releases of Ca from the SR being able to amplify the Ca-release process. Its findings chimed perfectly with Michael Stern's theoretical analysis (1992, *Biophys J* **63**, 497-517) that defined the requirements for 'local control' of Ca release by CICR: fuzzy space wasn't fuzzy logic at all. The images of highly localised releases of Ca ions from the SR into restricted spaces (obtained by means of a Ca fluorophore loaded into single cardiac myocytes and viewed via a laser scanning confocal microscope) provided a highly pleasing result, both aesthetically and scientifically. The spark (in its macro form) provides a sufficiently large and rapid $\Delta[Ca^{2+}]$ near the SR Ca-release channel to account for the CICR process characterised by Fabiato. This scientific spark has led so far to a >600 paper explosion including many other tissues than cardiac muscle. Sydney Ringer would have been thrilled.

Cheng H, Lederer WJ & Cannell MB (1993). Calcium sparks: elementary events underlying excitation-contraction coupling in heart muscle. *Science* 262, 740-744 (cited >640 times).

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In our next issue, Peter Ellaway highlights his 10 key papers in neurophysiology

EESI-View

Portland Press has launched Enhanced Electronic Serials Interface (EESI-View), a new way of viewing journal articles on screen.

EESI-View employs a 3-frame approach to solve the frustrations of reading journal articles online, enabling the reader to view text, figures and author information at the same time, analogous to the printed page, with easy automatic resizing of frames, simple navigation, linking roll-overs to authors' affiliations and references, all customizable to suit the reader.

EESI-View was launched at BioScience 2004, the annual international meeting of the Biochemical Society, in Glasgow in July and will first be available for the *Biochemical Journal* Reviews.

UCLA physiologist honoured

Ernest Wright, professor of physiology and Melinkoff professor in medicine at the David Geffen School of Medicine at UCLA, has been

Ernest Wright, double award winner

named one of five 2004 Fellows of the Biophysical Society. His research team identified a new protein that senses changes in glucose, which could lead to the development of new drugs to control diabetes and obesity.

Janssen Pharmaceutica also presented Ernest Wright with the 2004 Janssen Award in Gastroenterology for a lifetime of achievement in the digestive sciences. The award was presented at the annual meeting of the American Gastroenterology Association in New Orleans.

Sun, sea, sand ... and physiology?

Jon Kibble starts the new term at St George's University in Grenada

Physiology Faculty (left to right) - Loren Nelson, Jon Kibble and Penny Hansen
Neuroscience & Department Chair (far right) - Randall House

I am Course Director for Medical Physiology at St George's University. We are located on the island of Grenada in the Eastern Caribbean, at the southern tip of the Windward Islands, about 100 miles north of Venezuela. Each summer we have 2 months leave (thank you Mr Chancellor!), from which I have just returned. This year I spent the time in Newfoundland, Canada, where I was able to engage in some educational research with the help of a grant from the American Physiological Society. My wife had our second child during the break (excellent timing dear), which kept us from having a rest. What follows is a record of my activities during the first week of the new term.

Monday

Today would have been the first day of term if it were not the Grenada Carnival national holiday. A procession from the capital, St George's, this afternoon was the culmination of a week of intensive partying and celebration across the country. Sadly I was in the office readying things for classes tomorrow. The task list was familiar to those who teach physiology and included preparing course handouts, re-sit examinations and updating our course website. The loss of my unique dancing style at the Carnival celebration was a blow it will doubtless survive.

Tuesday

I kicked off the course this morning with two introductory lectures on homeostasis and communication. At St George's University we have a traditional style medical curriculum, with the first 2 years concentrated on basic sciences. Our course is lecture based, supplemented with small group laboratory classes and clinical case tutorials. The course runs in tandem with neuroscience and immunology. Together with two full time colleagues, Penny Hansen and Loren Nelson, we teach the course twice a year to classes of around 300 students.

The afternoon was spent in office hours discussing the day's topics with students. I am constantly impressed by the students' insightful questions, coupled with their industry and enthusiasm. I recall a conversation with Dave Potts from Leeds some years back, in which he tried to explain to the then-bench-research-obsessed-me that teaching the kind of students we encounter is both a privilege and a pleasure. Thanks Dave, you were right.

Wednesday

This morning witnessed two more lectures from me, this time on membrane transport phenomena. Walking from my office to the lecture hall across campus I was struck yet again by the beauty of our setting. We are located on a peninsula at the south of the island called True Blue with panoramic views of the ocean and mountains. As an Englishman living in the West Indies it is about time I mentioned the weather (sorry). Our normal weather is about 80^{o} year round with a sea breeze. Perhaps Jane Austin was in Grenada when she wrote: 'What dreadful hot weather we have! It keeps me in a continual state of inelegance.' T-shirt, shorts and open sandals may be inelegant but are thankfully acceptable at almost all social events. A truly advanced culture.

During the afternoon, space between student appointments was taken trying to complete a paper review for an

Partial view of the Upper Campus (Physiology is the leftmost building) viewed from the University beach

education journal. I am mildly embarrassed by how little I knew about teaching while practicing the art as a new lecturer in the UK. Another 10 years and I just might have some idea. At SGU opportunities for research and scholarship arise through our Graduate School. Already established in areas like tropical medicine and parasitology, more programmes are developing. Incidentally, if anyone wants to develop a joint programme in physiology let me know (so long as your director of teaching is not hoping to make a fortune from it).

Thursday

Just one lecture this morning on membrane potentials. The rest of the morning was taken up finding my feet as incoming Chair of the Student Academic Affairs Committee. This is one of several committees that feed into our Faculty Senate, which in turn addresses the University Administration with a fighting chance of changing University policy. I enjoy this Committee because the students are a great source of constructive feedback and are also more likely than most academics to conclude a meeting on time with actionable items arising.

In addition to student office hours we met with our clinical tutors this afternoon to plan next week's laboratory class on electrocardiography. This is a significant logistical exercise with 30 small groups. We depend on local physicians to help us as facilitators and we meet with them each week to plan their role in the following week's session. We have a stable group including anaesthetists (good physiologists, Tony Angel assures me), community based physicians and surgeons. They are a great source of applied physiology and, like most West Indians, deeply knowledgeable about cricket. Their morale was shaken during England's majestic 2004 winter tour victory here, which I try not to mention more than weekly.

The island interior and rain forest

Friday

The students felt the misfortune of it being Friday the 13th this morning after my decision to include Donnan Equilibria in their physiology lecture. The rest of the morning was spent in a 3 hour planning and training session for our impending leap into e-learning using a new course management system called ANGEL. All very exciting, though slightly daunting to now become webmaster armed only with a rudimentary knowledge of Microsoft Office. Our IT support is fortunately excellent so no sleepless nights are expected.

This afternoon's office hours ended at 4 pm to give time for an important decision – where to head for a cocktail or two. I opt again for Coconut Beach to join a group united not through where we work but by ownership of boisterous children. They play at the beach while the adults watch the sun go down and reflect on a pleasant week in Grenada.

Thanks are owing to Roger Green, my mentor and PhD supervisor and the physiologists at Manchester in the early 90s who introduced me to the excitement of our discipline. Also to Pete and Jackie Hardcastle, Roy Levin and other role models at Sheffield for their outstanding professionalism and enthusiasm for teaching physiology.

Grenada is a wonderful venue for a winter holiday. If you pass this way do call and I will be happy to show you around.

Jon Kibble
Medical Physiology Department of Physiology and Neuroscience, St George's University
Grenada, West Indies

Grand Anse beach, taken from the University satellite campus

Postscript – 14 September

I wrote the diary above around the middle of August. It seems a lot longer ago now.

Today is one week since Hurricane Ivan made a direct hit on Grenada. I am writing from my in-laws home in Devon, having evacuated my family from Grenada three days ago via Barbados. Our home was badly damaged during the storm, with large sections of the roof parting company with the walls while we attempted to shelter inside the one storey

construction. Luckily one room remained safe and dry until the storm ended. Next morning as we ventured out to assess the damage and to find friends it was clear most

Grenadians had been less fortunate. The majority of homes were completely destroyed, a large fraction of the population was homeless and some had lost their lives.

Two days after the storm we were able to drive to the University Campus for the first time. Most buildings there were in good shape, being of recent high quality construction. More importantly, the students had responded magnificently to the emergency. Student government had organized food, housing, security and were instrumental in orchestrating an evacuation plan. We hope to resume teaching soon, although it may be at a site in the US for the rest of the semester.

At this moment Grenada is badly broken. It will be fixed. The tenacity of the Grenadian people and their partners, like St George's University, will see to it. However, a great deal of help will be needed from the international community too. So, amongst all the other good causes, please do not forget the people of Grenada.

Jon Kibble
St George's University, Grenada, Windward Islands

Note: Hurricane Ivan damaged or destroyed nearly 90% of all Grenada's buildings, and left almost 10% of the population living in temporary shelters. By 17 September the death toll had risen to 37. Anyone wanting to make donations to help the rebuilding effort should contact:

Grenada Damage Relief Fund on 020 7631 4275 (in the UK).

People specifically wanting to help St Georges University should look on their website at www.sgu.edu.

US-based Members can also contact the SGU Relief Fund for Grenada, c/o 1 East Main Street, Bay Shore, New York 11706, USA.

Researchers in Residence

Pupils from Tytherington High School, Macclesfield with their teacher, Katherine Stokes (left), and Kathleen Griffin (right)

With so much emphasis at the moment on the 'public engagement of science', I decided to get involved at the grass roots level and join the 'Researchers in Residence' programme. Funded by the research councils and managed by Sheffield Hallam University, this scheme encourages postgraduate and postdoctoral scientists to spend time in a local secondary school. The 24 hour school placement can be carried out over any time period and researchers can lead any activities. However, one key aim of the placement is to crush any stereotypes of stuffy scientists and provide pupils with a positive role model for doing scientific research.

Staff at Sheffield Hallam offer full support throughout the placement and provide lots of ideas of what to do with the school pupils. I've met other researchers who've led revision lessons for A Level students leading up to exam time, talked about careers in science, debated animal welfare issues and talked specifically about their research. At my host school, Tytherington High, a specialist science school in Macclesfield, they had a more definite idea of what they wanted me to do. I spent 3 hours a week developing a research project with pupils for entry into the AstraZeneca Science Challenge.

I spent a term with a great bunch of Year 10 pupils, advising them on how to plan, conduct and present scientific research. In conversation I spent a lot of time discussing my own research with them and found that they were all genuinely very interested in what I did. While this was very challenging I felt this improved my communication skills tremendously. This was the first time many pupils had thought about what life would be like as a scientist. Many were surprised that science was something people did all day every day, and not just for 2 hours a week. None of them seemed to be put off!

The pupils were very enthusiastic about their research project *In One End and Out the Other*, where they investigated the optimum conditions for lactase to work and explored lactase deficiency. After a poster presentation and grilling from the judges they won both their heat and the overall prize at the AstraZeneca Science Challenge. Additionally, my time at the school will have hopefully had a more lasting influence on the pupils. I'd like to think that I'd given them a realistic impression of what it's like to be a young scientist and even encouraged some of them to study science at a higher level. Personally, I got so much out of the scheme. As well as boosting my CV and developing my own interpersonal skills, a bit of time out of the lab helped me become more focused on my own work. Most of all, it was great fun!

Whilst it can seem so overwhelming undertaking a PhD, I'd highly recommend making the time to become a Researcher in Residence. It will boost your transferable skills, you'll be an asset to your host school and more importantly, you'll enjoy it. For more information please look at the website: http://extra.shu.ac.uk/rinr/site

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Doping – a misuse of science

In the last of our series of articles on exercise physiology in the Olympic year, Craig Sharp looks at doping issues

Craig Sharp

Many of the recent Olympic headlines featured aspects of doping, which in essence is the taking of substances, mostly specifically banned by the Olympic Charter, to 'artificially improve competition performance'. Competitors are not necessarily looking for major performance improvements through doping, because very small increments often make a critical difference in elite sport - as the closeness of the British wins in Athens in the rowing four and the men's 4 x 100m relay and Kelly Holmes in the 800m, testify. The men's relay team got home by .01s, the same margin by which Said Aouita in1984 broke David Moorcroft's 5000m world record of 13min 0.41s. In the latter case, the margin was 0.000013%, less than the accuracy of the track measurement (Sharp, 1999)! Such fine margins provide a strong temptation to resort to doping in the quantified sports. The saddest case among the dozen or so disqualified competitors at Athens was Irina Kozhanenko who 'won' the shot-putt, the only event staged in Ancient Olympia, before 18,000 spectators. However, she tested positive for the anabolic steroid stanozolol – the same drug that Ben Johnson had taken 16 years before. The first world anti-doping conference, in Lausanne in 1999, stimulated by the doping debacle of the 1998 Tour de France when the entire Festina team was disqualified, led to the world anti-doping agency (WADA) being set up, with former IOC acting-president Dick Pound, a former Olympian, elected as a strong president. Below will be discussed three major doping aspects, regarding muscle, blood and the genome.

Muscle

Competitors seek to induce muscle hypertrophy by variously utilising growth hormone (hGH), anabolic steroids, 'designer steroids', or possibly in the future by inhibiting myostatin, the muscle's normal limiter. The main reason for the popularity of hGH was that it has been hitherto undetectable. However, Peter Sonksen has headed a team which developed a test for use in Athens. Anabolic steroids have been in sport for several decades; the main problem with the detection of such hormone-based drugs has been that they are used mainly during strength-training mesocycles in a periodised training regimen, which usually occur months before competition. However, 'out-of-competition' testing, where available, has helped to cut down their use. Nevertheless, the athletes (or rather the illegal laboratories) have responded by synthesising 'designer' steroids, the design being to foil the test procedures. In June 2003 the USA Doping Agency was tipped off via an anonymous syringe, which they sent on to Don Catlin's Olympic analytical laboratory at UCLA, where it was eventually identified as containing tetrahydrogestrinone (THG), related to the banned anabolic steroid gestrionone (Knight, 2003). However, the standard test for steroids has initially involved a gas chromatography scan, with fine tuning by mass spectrometry. Normally, appropriately prepared steroids show a sharp chromatograph peak – but in the case of THG there was only a couple of dozen small peaks, i.e. a negative result on the first screening, hence the analysis would not normally be taken further. Other designer doping agents no doubt exist. While not 'designed', Nandrolone is a steroid which has been newsworthy in the past few years, partly because it seems that some legitimate ergogenic 'supplements' (e.g. creatine) have been deliberately contaminated with nandrolone, to increase their efficacy, and hence sales. This may have led to doping tests on some competitors being positive, but at levels only marginally above the designated threshold.

Myostatin is a compound whose normal function is to limit muscle growth, by effectively down-regulating satellite cells. The Belgian Blue breed of beef cattle is genetically deficient in myostatin, and consequently looks like the bovine equivalent of hypertrophic bodybuilders. A similar (rare) condition has been reported in humans, and there is anecdotal belief that, over the years, some weightlifters have had the syndrome. However, were an artificial myostatin inhibitor to come onto the (black) market, muscle hypertrophy could possibly be taken to new limits. Roger Harris of Chichester notes that the current emphasis on gross muscle development of body-builders may already lead to their approaching the limits to which muscle may hypertrophy, before suffering the human equivalent of Green Muscle Disease of turkeys, a deep pectoral myopathy involving focal necrosis, which tends to occur in turkeys of above 80kg live-weight.

Belgian Blue beef cattle look like the bovine equivalent of hypertrophic bodybuilders

Blood

Erythropoeitin (EPO) is a juxta-glomerular anti-apoptopic agent that stimulates erythroid progenitor cells. It is upregulated in hypoxic conditions

including altitude, resulting in enhanced erythropoiesis. The resulting rise in circulating haemoglobin increases the oxygen carrying capacity of the blood. Endurance athletes use recombinant EPO (rHuEpo) to increase their maximal oxygen uptake, as did the banned Festina cycling team mentioned above. Similarly, last month, UK cyclist David Miller was stripped of his World time-trial title, and banned for 2 years. Oddly, even athletes in the sprints and power events (e.g. USA sprinter Kelli White) have taken rHuEpo, suggesting another possible doping effect unconnected with erythropoiesis.

The detection of rHuEpo has proved difficult, and setting a haematocrit ceiling is very unsatisfactory, for example where altitude may have been an influence. However, due to their structural microheterogeneity, natural and recombinant EPO comprise several isoforms, some of which have charge differences, and can be differentiated by isoelectric focussing in urine analysis (Lasne & de Ceaurriz, 2000), although this is only effective up to 3 days after taking rHuEpo. Alternatively, my PhD student Brian Moore, among others, is researching the use of reticulocyte profiling and analysis as a possible means of somewhat longer-term detection.

However, artificial oxygen carriers (both haemoglobin based, e.g. Hemolink, and perflurorocarbons, e.g. Oxyfluor), are increasingly being developed and used, and the athletes are also tending to revert to the less detectable autologous 'blood doping' (the venesection and storage of one or two units of blood and their re-transfusion some 4 weeks later). The overall response of the dope-testers must be to increase out-of-competition testing and to institute haematological passports, in targeted sports.

The genome

Although not yet a reality as far as is known, 'gene doping' is defined by WADA (2004) as 'the non-therapeutic use of genes, genetic elements and/or cells, that have the capacity to enhance athletic performance'. Montgomery *et al* (1998) were the first to provide clear evidence of a 'fitness' gene, namely the ACE-II insertion 287 base-pair allele giving lower angiotensin converter enzyme activity, with enhanced endurance performance (possibly through improved mitochondrial function). Now a considerable number of genes influencing physical fitness parameters are known.

Genes have already been introduced to human patients with, for example, immune deficiency syndromes, with some success. Also, Sweeney (2004) has used an adeno-associated virus (AAV, which infects muscle, harmlessly) as a vector for a synthetic gene coding for insulin-like growth factor 1 (IGLF-1), that triggers replication of muscle satellite cells, which stimulate muscle hypertrophy. His group injected AAV-IGLF-1 into the muscle of one leg in rats, then strength-trained the rats. After 8 weeks the experimental muscle showed nearly twice the strength gains of the control legs; even sedentary treated rats showed a 15% increase.

Experiments on mice genetically engineered to produce less effective myostatin (see above), have shown that diminishing this anti-growth factor induces both hypertrophy and, unusually, muscle hyperplasia, again possibly through up-regulating satellite cell behaviour. Another natural fitness gene is one that appears to positively influence the EPO receptor, as in Eero Maentyranta, who won two cross-country skiing events at the 1964 Winter Olympics and who, with members of his family, was found to have such a mutation. Elemans *et al* (2004) recently reported on a 'superfast' muscle' in the syrinx vocal organ of the ring dove; might the code from that be utilised for human sprinters?

The integration of genome datasets with physiological performance parameters is in its infancy, but will accelerate; and it is not only the encoded protein itself, but its rate of transcription, that is also important, so aspects of gene expression profiling may also come to be of use to sports competitors, possibly legitimately. Just as pharmacogenetics may usefully elicit differences in response to medicinal drugs in patients, so a form of athleticogenetics may help coaches to optimise training very specifically. All that would seem to lie some time in the future, although Theodore Friedman, member of the WADA committee believes that gene doping will occur 'sooner than people think', (in Beijing in 2008 perhaps?), and Peter Schjerling from the Copenhagen Muscle Research Centre, speaking at the 2001 London conference on genes and sport, indicated that such 'gene doping' could be near-impossible to detect. The induced cell signals or products are indistinguishable from natural equivalents, and may not enter the blood.

In conclusion, although the measured sports, especially, are tainted by doping, which in part is a result of sheer commercialism, there are overall, in a range of sports as wide as in the Summer and Winter Olympic Games, thousands of superb displays of skill and tenacity from utterly dedicated 'clean' competitors. Let us hope that most of them in the future will still be able to say, with Addison: 'Tis not in mortals to command success, but we'll do more, Sempronius, we'll deserve it.'

Acknowledgement

It is a pleasure warmly to acknowledge help from my excellent research students Brian Moore and Isabel Woodman.

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Top: Claude Duchamp (left) and Martin Brand
Centre: Brigitte Sibille (left) and Jean Louis Rouanet
Above: Benjamin Rey (left) and Nicolas Hanuise
Below: Darren Talbot blends in


Mitochondrial proton conductance in cold adapted king penguins

Keeping warm is a serious business. And there is more to it than fast swimming and a warm coat

Immersion in cold water is one of the most stressful situations encountered by endotherms because of the large thermal gradient and the high thermal conductivity of water. Warm-blooded animals adapted to sea life, such as penguins, must have developed powerful physiological adjustments to withstand this massive energetic challenge by reducing heat loss and by generating heat for regulatory thermogenesis. Heat production through the vigorous physical activity of swimming would not be sufficient as it also raises heat loss severalfold. There is, therefore, more to keeping warm in cold sea water than just physical activity and thermal insulation with fat and dense, waterproof feathers.

The adaptive thermogenic mechanisms developed by marine birds are much less understood than those in mammals, which possess specialized thermogenic brown adipose tissue. In brown fat mitochondria, heat is generated by regulated uncoupling of substrate oxidation and ATP synthesis, catalyzed by a specific mitochondrial protein called uncoupling protein 1 (UCP1). UCP1 increases the proton conductance of the inner membrane and is activated by fatty acids and inhibited by purine nucleoside di- and triphosphates (Cannon & Nedergaard, 2004). Birds lack brown adipose tissue, and instead have uncharacterized adaptive thermogenic mechanisms in skeletal muscle (Duchamp & Barré, 1993). Recently, a homologue of mammalian UCPs has been characterized in avian skeletal muscle, but its biochemical roles remain hypothetical (Raimbault *et al*. 2001; Talbot *et al*. 2003).

Are functional UCPs expressed in skeletal muscle from king penguin juveniles? And do they contribute to the adaptive thermogenic mechanisms developed during cold sea adaptation (Barré & Rousset, 1986)? Young king penguins spend their first year on land, protected by a thick insulating down and fed periodically by their parents fishing at sea. Only after moulting at age 12-13 months do they face the thermogenic challenge of passage from shore to marine life in cold subantarctic seawater at 4-6°C. Interestingly, this transition is progressive and requires several acclimation journeys into the sea. This suggests that it involves some specific adaptation that takes time to fully develop.

Talbot *et al*. (2004) compared three groups of young moulted penguins: juveniles that had never been to sea, juveniles that were naturally adapted to marine life and juveniles that were experimentally exposed to 10 successive 5 hr cold-water immersions at 8°C every second day to reproduce sea acclimatization. Skeletal muscle mitochondria isolated from pectoralis muscle biopsies exhibited two different adaptive mechanisms that increased mitochondrial inner membrane proton conductance and thus are potentially thermogenic: the first involves the avian UCP and the second involves the adenine nucleotide translocase (Fig. 1).

The presence of functional UCP was assessed by the demonstration of superoxide-stimulated, GDP-inhibitable proton conductance across the mitochondrial inner membrane, a common feature of all known UCPs (Echtay *et al*. 2002; Talbot *et al*. 2003). Muscle mitochondria from never-immersed juveniles did not have functional UCP, while those from immersed penguins did. Interestingly, experimental immersion in cold water was sufficient to trigger muscle biochemical adaptations. In parallel, the mRNA for penguin UCP was markedly increased in skeletal muscle from both experimentally and naturally immersed juvenile penguins.

A second mechanism catalyzing proton translocation through mitochondrial membranes involves the adenine nucleotide translocase (ANT). In the

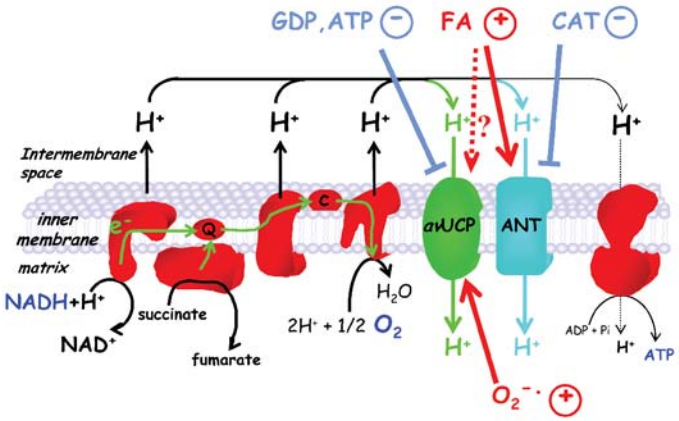

Figure 1. Scheme of the putative roles played by penguin uncoupling protein (avUCP) and adenine nucleotide translocase (ANT) on mitochondrial inner membrane proton conductance. Electron transfer from NADH to O_2 along the respiratory chain is linked to the generation of a proton electrochemical potential gradient. Proton re-entry can occur through the ATP synthase to generate ATP or may be catalyzed by specific proteins avUCP and ANT, producing heat. The activity of avUCP and ANT can be modulated by superoxide, fatty acids and purine nucleotides by still hypothetical mechanisms. Carboxyatractylate (CAT) is a specific ANT inhibitor.

presence of fatty acids, mitochondria isolated from artificially or naturally immersed juveniles showed a greater carboxyatractylate-sensitive ANT-catalyzed proton conductance than those from never-immersed penguins. This was due to an increase in ANT content as indicated by carboxyatractylate binding and western blots.

Further studies are needed to investigate whether the proton conductances of penguin UCP and ANT are switched on after cold-water immersion as part of thermogenic acclimation and/or to protect against oxidative damage by reducing the production of endogenous reactive oxygen species (ROS) likely to be generated during anoxia/reoxygenation episodes occurring with diving. However, these data represent a breakthrough, as they show for the first time the existence of UCP- and ANT-catalyzed modulation of the proton conductance of the mitochondrial inner membrane in naturally cold-adapted young birds. Further, the fact that such uncoupling of oxidative phosphorylation in skeletal muscle mitochondria can be induced by natural or experimental repeated immersions in cold-water underlines its adaptive value for facing a major cold challenge at a crucial time in penguin life.

Acknowledgements

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APS launch *Physiology*

The American Physiological Society (APS) and the International Union of Physiological Sciences (IUPS) relaunched *News in Physiological Sciences* (NIPS) in August as a new bimonthly journal, *Physiology*.

Physiology (latest cover illustrated below) contains invited articles to identify, review and critically discuss research and developments in the broad, integrative science of physiology.

Walter Boron (Yale University School of Medicine) is the Editor, with Michael Caplan (Yale) and Ulrich Pohl (University of Munich) as

Associate Editors. Walter was previously Editor of *NIPS* and was also on the Editorial Board of *The Journal of Physiology* from1985 to 1992.

APS Legacy Project

The American Physiological Society has recently completed its *Legacy Project*, a mission to share more than 100 years of physiological research. To celebrate this arduous project that included scanning original journal volumes dating back to 1898, the APS has identified 46 'historic breakthrough' research articles, with additional commentary about the work and times from the original authors, where possible. For free access visit the APS website at:

http://www.the-aps.org/publications/classics/

Understanding standing

Standing is something we do without conscious thought, but it is a complex task involving the nervous system, muscles and tendon properties - and anticipation! Martin Lakie and Ian Loram explain

Martin Lakie (top) and Ian Loram (above) propose that the increased force that is required to prevent collapse is associated with active shortening of the muscles

In standing the body's centre of mass (the imaginary point at which the mass of the body can be considered to be concentrated, approximately in the small of the back) is usually slightly forward of the ankle joint which forms the axle on which the body rotates (Fig. 1*A*). So it is literally true to say that we are all inclined to fall on our faces. Why does this catastrophe not occur? The answer is that calf muscles, gastrocnemius and soleus are responsible (Fig. 1*B*). Gravity pulls us down and consequently forward and these muscles pull us up and consequently back. The more we lean forward the harder they have to work. Studies have shown that for most people the angle of forward lean is about 3 degrees. At this angle the mean force in the calf muscles of each leg is about 500 N, which is about 12% of the maximal force that can be produced by a single soleus muscle (figures from Hoy *et al.* 1990). Due to the muscular activity the total metabolic energy needed to stand is about 25 W greater than for lying supine (Davidson & Passmore, 1966). Although the anatomy seems simple, the problem that has intrigued neurophysiologists for many years is precisely how standing people unconsciously regulate the activity of the calf muscles in response to the gravitational requirement. [1]

The inverted pendulum

In attempts to answer this question, researchers have used a simplified model to represent human standing. The concept is shown in Fig. 1*B*. At the outset, it must be admitted that this model does not preserve all the normal features of standing. An assumption is made that all the motion occurs solely at the ankles – i.e. there is no other movement of the limbs or between different segments of the body. Also, it is usual to consider movement in only the forward – back (antero-posterior) plane whereas there is also the problem of side-to-side motion of the body to be considered. Furthermore, the model assumes that the two ankles share a common axis. Observation will show that this is not the way that most people stand. Nevertheless, since its introduction by Smith in 1957 (Smith was a lecturer in Anatomy at the University of St Andrews) the inverted pendulum concept has been a powerful stimulus to explaining how standing works. It is a good example of a reductionist approach where, in order to understand a complicated system, we may remove some of its complex features and study a simplified version. Many studies have confirmed that the fundamental problem in standing is balancing an inverted pendulum. Although human standing is something that we mainly take for granted it is a complex activity that takes all of us about a year of life to accomplish. It is a reasonable hope that by understanding how the inverted pendulum is balanced we will be able to understand howstanding in particular, and other aspects of postural maintenance in general, are controlled.

Sounding sway – a new technique for observing muscles in action

A number of measurements have conventionally been made on standing subjects in attempts to understand the standing process. It is universally agreed that in standing the body is not static. The human inverted pendulum is inherently unstable and small slow irregular sways are continually observed. Thus, body angle, torque and EMG continually fluctuate. It is comparatively easy to measure the muscle forces (or more precisely their close relative the ankle torques). With a little more difficulty the change in body angle can be measured. As far as

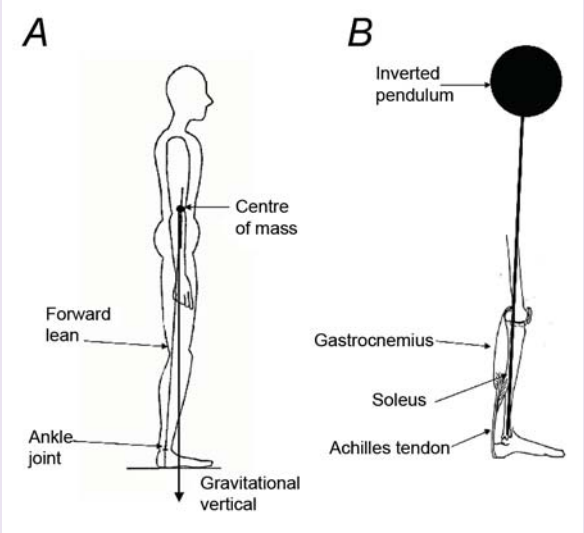

Figure 1. *A* The standing human. The centre of mass is normally forward of the axis of rotation (the ankles). Consequently the body tends to topple forward. *B* Collapse is prevented by the activity of the soleus and gastrocnemius muscles. The anterior compartment muscles (principally the tibialis anterior) are generally silent in quiet standing. Movement is assumed to occur only at the ankles and the body can therefore be considered as an inverted pendulum.
(Fig. 1a adapted from Winter *et al.* 2001)

[1]For simplicity, we mention only forward sway (falls) in this article. Backward sway (throws) are an identical process, with the signs of the movements reversed.

the muscles themselves are concerned it has previously only been possible to record their EMG. This enables one to see how their activity is varying, but it does not let one see what they are actually doing In this article we describe a new technique which allows us to observe the tiny movements of calf muscles in standing subjects. The new information obtained by this technique suggests that many current ideas about standing require revision.

Our approach to the problem has been the use of dynamic ultrasonography with computerized image analysis (Loram *et al.* 2004). The work was done in collaboration with Constantinos Maganaris at Manchester Metropolitan University. Ultrasound is strongly reflected by collagen fibres. The collagen in tendons shows up clearly and collagen also demarcates many of the muscle fibres. This technique has previously been quite extensively used to make static measurements of muscle and tendon lengths. The pointwise resolution of the technique depends on a number of factors including the frequency of the ultrasound and is typically about 0.5 mm.

However, the ultrasound image has the properties of an array of detectors. This considerably increases the resolving power of the technique. As a simple analogy the human eye will struggle to see a dot of 10 mm diameter at 6 metres range – stretch the dot out into a long line 10 mm wide (power cable) and it may be seen at several kilometers. We have used computerized image analysis to take advantage of this fact. It is possible to resolve muscle fibre length changes of as little as 10 µm in the calf. A typical static image of the calf muscles is shown in Fig. 2.

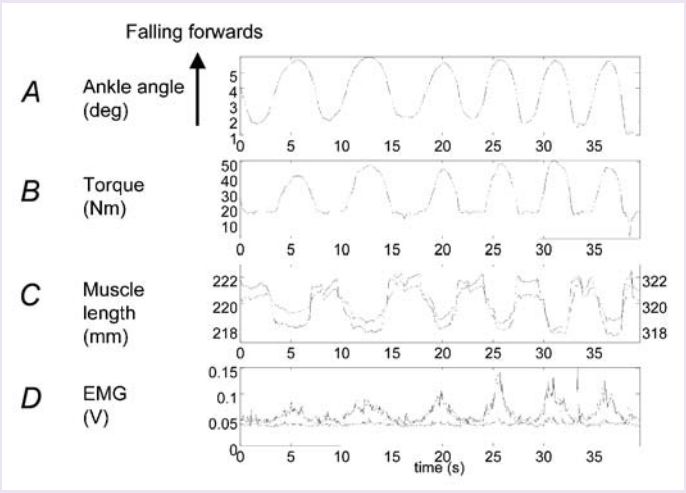

Figure 3. Slow voluntary sways of a typical subject. Measurements were made on the left leg. Ankle angle is shown in (*A*) and ankle torque in (*B*). As is anticipated, torque rises as the subject leans forwards. (*C*) shows the changes in length for gastrocnemius muscle (continuous line) and soleus muscle (dotted line). Muscle lengths are expressed relative to typical mean muscle lengths of 320 mm and 220 mm for soleus and gastrocnemius respectively. Both muscles shorten as the subject leans forward. (*D*) Integrated EMG for gastrocnemius (continuous line) and soleus (dotted line). An increase of EMG is associated with muscle shortening and rise in torque. Adapted from Loram *et al.* (2004).

What might happen in standing – orthodox views

Consider Fig. 1*B*. As the body sways forwards the muscles are stretched.

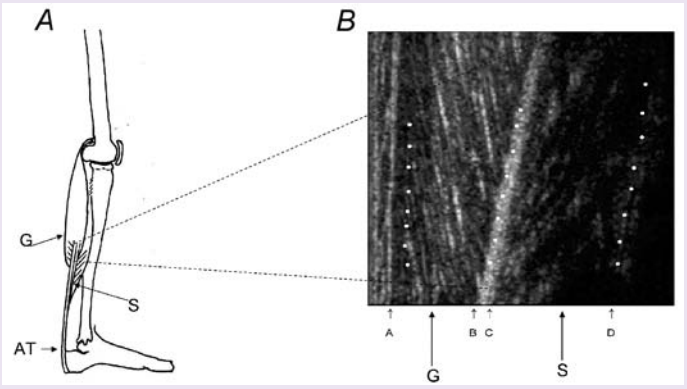

Figure 2. A static ultrasound image. *A* The calf muscles gastrocnemius (G) and soleus (S) and the Achilles tendon (AT) showing the approximate point at which a parasaggital plane image was obtained by ultrasonography using a dynamic ultrasound scanner (ATL, HDI 3000). *B* The resulting image which was approximately 7 cm square. A is the proximal aponeurosis (thin sheet of inextensible connective tissue linking muscle and tendon) of gastrocnemius muscle and B the distal aponeurosis of gastrocnemius. C is the distal aponeurosis of soleus and D is the proximal aponeurosis of soleus. The white streaks within the muscle are collagen fibres which demarcate some of the muscle fibres. Movements of the muscle fibres were recorded by automatically tracking eight pairs of markers (white dots) using 2-D cross correlation analysis on successive frames. Vector analysis was used to resolve the movement of the markers into length changes of the muscles. Adapted from Loram *et al.* (2004).

Ankle torque (muscle force) rises (it has to or you fall down). One school of thought (e.g. Winter *et al.* 2001) has long maintained that the active muscles produce the force automatically as a direct consequence of the stretch because they have spring-like properties. If the spring stiffness is adequate, the force that can be generated by muscle stretch will suffice to prevent a fall. The job of the nervous system is simply to set the resistance to stretch of the muscles to a sufficiently high value; then no further neural intervention is needed. This *mechanical tonus* theory could be stated as '*increased force is generated by muscle stretch*'. Others have maintained that the mechanical tone of the muscles is inadequate to produce stability. They also observe that forward sway is associated with an increased EMG in the muscles (e.g. Morasso & Sanguineti, 2001; Fitzpatrick *et al.* 1994). Accordingly, they suggest that stretching the active muscle will generate stretch reflexes that raise tone by increasing activation of the stretched muscle. This *reflex tonus* view, summarised by the Sherrington School in the 'little red book' (Creed *et al.* 1932), is that '*increased force is produced by muscle stretch plus reflex activity*'. Both theories assume that the muscle will be lengthened by forward sway.

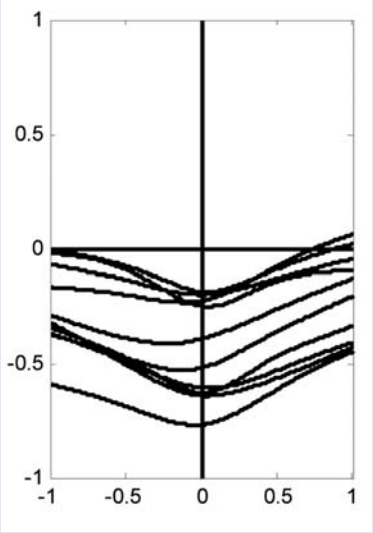

Figure 4. Cross correlation of soleus muscle length against ankle angle for eleven subjects standing normally. The tiny movements of the soleus muscle are on average in the opposite direction to that of the body. If they were a perfect mirror image the value of the cross correlation would be – 1.0 and the delay zero. They are in fact an approximation to a mirror image. The closest approximation occurs in subjects where the intrinsic ankle stiffness is lowest in relationship to their size and mass. Loram & Lakie (unpublished results).

What does happen in standing – paradoxical muscle movements revealed by ultrasonography

However, Fig. 3 shows that forward sway is in fact associated with a shortening of the muscle! Torque rises, EMG increases but the muscle shortens The rise in force cannot be due to muscle tone or muscle reflexes. The muscles and the load generally move in opposite directions.

This might at first seem not just counterintuitive, but quite impossible. How can it happen? The answer is that the stiffness of the Achilles' tendon and foot is not very great at the low forces that are involved in standing. (It is much greater for the large forces involved in running and jumping.) The tendon and the foot together form a spring-like buffer that decouples the muscle and the load (the body). This spring stiffness is not itself sufficient to permit standing. In direct measurements using a piezoelectric stretcher, we have measured the overall stiffness of the ankle. That is, we have abruptly stretched the series combination of the foot, the tendon and the muscle and measured the resulting force increment. This combination (inevitably limited by the weakest link) defines the intrinsic stiffness of the ankle. It represents the intrinsic stiffness because the value is obtained before the nervous system has time to alter the state of the muscle. For 10 subjects the average intrinsic ankle stiffness was only 91% of that necessary for standing (Loram & Lakie, 2002a). Using rather bigger stretches, Morasso's group (Casadio *et al.* 2004) have recently obtained an even lower average value of 64%. What this means in effect is that if the muscle remained stationary then stretch of the foot and tendon caused by a sway would generate only 64-91% of the force that is necessary to prevent falling. In order to supply the deficiency, additional stretch of the tendon and foot must be generated. This can only be produced by active shortening of the muscle. Thus, forward sway of the body stretches the tendon – foot spring. Muscle shortening also simultaneously stretches it. These two features acting in concert produce the necessary force for standing. Muscle movement is absolutely necessary and the job cannot be done statically. Figure 3 was obtained from a subject who was voluntarily making large sways. The same process has been observed in subjects standing normally. The body and muscle movements are naturally much smaller but they are clearly on average in the opposite sense (Fig. 4). We have called this process of control by active alterations in muscle length *the ballistic bias mechanism* (Loram & Lakie, 2002b).

It might seem that the shortfall in stiffness that must be made up by this mechanism is only 9-36%. However, the 100% figure applies to sways that are of infinite duration. For sways that take the times commonly observed in standing (usually ~0.8 s for a unidirectional sway) calculation and experiment suggest that a value of close to 200% is necessary (this figure represents what is often called the *effective* stiffness). Thus, the intrinsic stiffness of the ankle and the ballistic bias mechanism make a quantitatively approximately equal contribution to the effective stiffness. The intrinsic stiffness almost cancels the force due to gravity and the fine tuning is done by the active process. This probably means that the job of the nervous system is made easier.

Ballistic bias in action – acting on impulse

In an attempt to demonstrate the ballistic bias mechanism we have described some simple experiments in which subjects balance a large inverted pendulum by hand (Lakie et al. 2003). The pendulum represents the body. The hand represents the calf muscles. The hand is connected to the pendulum by a steel spring which defines the intrinsic stiffness. It can be set to any desired value. With values ~70-100% subjects can easily balance the pendulum by active hand movements although none of them were able to describe exactly how they did it. Analysis clearly showed that on average the hand and pendulum moved in opposite directions. However, at any instant the movements are not an exact mirror image. Like the body, the pendulum sways rather slowly with an average duration between turning points of ~0.8 s. The hand movements are faster and intermittent (occurring approximately every 0.3 s). Each hand movement is a ballistic bias adjustment (impulse).

The most basic behaviour of such a system would be a form of oscillation where each impulse violently catches

and reverses a fall, throwing the pendulum transiently more upright in the manner of someone balancing on a pogo stick or keeping a tennis ball in the air with a racquet. In reality, depending on the complexity of the task and the sensory information available to the subject, there are generally 2-4 bias adjustments per unidirectional sway. The impulses are smaller and more sophisticated than those made on a pogo stick – consequently they are not all successful (they may merely slow the pendulum but not reverse it).

This is a good strategy because by making the adjustments as small as possible the acceleration, and hence sway size, of the pendulum is minimized. The large inertia of the pendulum buys time for the process to be tried again. The duration of the pendulum sway can therefore be explained as a consequence of an intermittent impulsive discrete motor act taking about 0.3 s and usually needing repetition one or more times per pendulum sway in order to reverse it. It also suggests a plausible mechanism by which any preferred standing position may be preserved. The pendulum or body is moved to, and maintained at, a new position by a series of nudges. As the impulses involve active muscle length changes which are on average in the opposite direction to those that would be passively produced, they must be driven by a signal which anticipates pendulum movement. Muscle activity cannot be a simple reaction to muscle length or tension (if it were it would produce bi-stable or 'toggle' action in the muscle). Ballistic bias requires a higher level of control than has commonly been assumed for standing. We have recently been able to observe these ballistic bias adjustments of the calf muscles in normally standing subjects. They are very much smaller than the hand movements, but they have remarkably similar features.

Conclusion

Conventional views assume that the increased force that is required to prevent collapse is produced by stretching the active muscles. In opposition to this view we propose that the force is associated with active shortening of the muscles.

Furthermore, this is not a continuous type of feedback control arising from the muscles, but an impulsive controller which acts intermittently and anticipatorily. Many years ago, Craik showed that individually judged outputs of the nervous system could only be made at a low rate of 2-3 per second (Craik, 1947). The requirement for an anticipatory controller suggests a level of sophistication that is greater than the simple mechanical/reflex ideas that have been commonly proposed.

The place of standing in the hierarchy of motor control requires revision. In standing, cause and effect may have been confused; postural sway is actually generated by anticipatory neural activity whereas it has previously been assumed that neural activity is a reaction to postural sway.

Also, these observations suggest that the behaviour of muscles in other postural tasks assumed to be reflex should be investigated. 'Static' postural control may be a myth.

Acknowledgments

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The Journal of Physiology symposia

The Journal of Physiology will sponsor two symposia at the IUPS meeting to be held in San Diego, CA, USA from 31 March to 5 April, 2005.

***PDZ domain scaffolding proteins and their functions in polarized cells*, will take place on Monday, 4 April 2005 from 0800-1000 and speakers will include Mark Donowitz, Sharon L Milgram, Heini Murer and Edward Weinman. This symposium is organised by Mark Donowitz and Yoshihisa Kurachi on behalf of the Editorial Board of *The Journal*.**

***TRP channels: physiological genomics and proteomics*, is scheduled for 1515-1715 on Tuesday, 5 April. Bernd Nilius, Wolfgang Liedtke, Viet Flockerzi and Craig Montell will speak. Stewart Sage and Bernd Nilius will act as organisers for the Editorial Board**

The proceedings of the 2004 *Journal* symposia – *Structure/function correlates in neurons and networks: a symposium in honour of the late Eberhard H Buhl** held in Leeds, UK on 10 September, and *The senses*, held in San Diego, CA, USA on 22 October – will be published in early issues of *The Journal of Physiology*.

See p... for a symposium report

Reciprocal communication between L-type Ca^{2+} channel and ryanodine receptor in frog skeletal muscle

During skeletal muscle activation, L-Type Ca^{2+} channel opens the ryanodine receptor. In turn, the ryanodine receptor changes the properties of L-Type Ca^{2+} channel

Top: Roberta Squecco (left) and Chiara Bencini
Left: Claudia Piperio (above) and Fabio Francini (below)

Depolarisation of the surface membrane in skeletal muscle fibres causes the excitation-contraction coupling (ECC) by triggering a series of events that ends with the contraction of the fibre. Depolarisation propagates as an action potential into the fibre via the T tubular system (TT) where the dihydropyridine receptors (DHPR) lie arranged in tetrads. Each unit of the tetrad is also a voltage operated L-type Ca^{2+} channel (L-CaC) (Fig. 1), consisting of five subunits: α_1, α_2, β, γ and δ. The pore-forming unit α_1 has an aminoacidic sequence organized in four repeated domains (I, II, III, IV), each containing six transmembrane segments (S1-S6). The S4 segments contain positively charged aminoacid residues (yellow cylinders in Fig. 1). When the TT membrane is depolarised the charged S4-segment senses the new potential and moves. This movement, recorded by electrophysiological techniques, is called intramembrane charge movement (ICM). ICM determines the opening of the L-CaC and the movement of the loop between the II and III domain. Consequently, the coupled ryanodine receptor/Ca^{2+}-release channel (RyR/CRC) of the sarcoplasmic reticulum (SR) opens and the luminal Ca^{2+}, stored in the SR can flow into the myoplasm (Figs. 1 and 2).

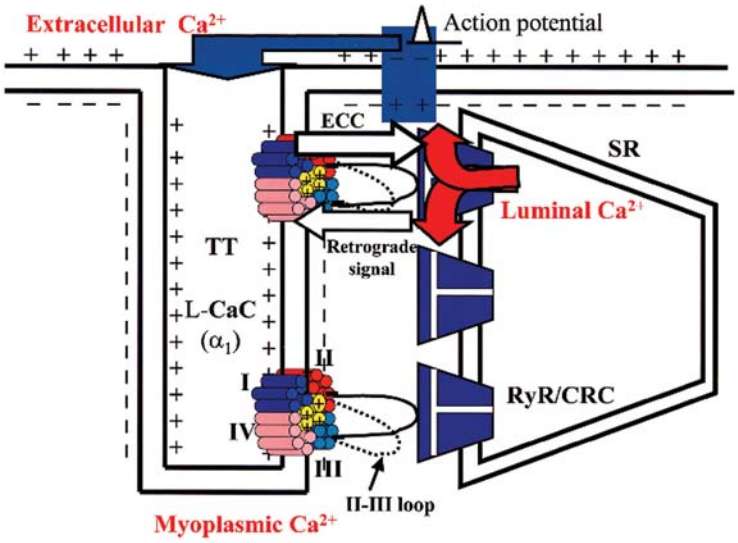

Figure 1. Schematic representation of excitation-contraction coupling (ECC)
Depolarisation propagates as an action potential into the fibre via the T tubular system (TT), where the L-CaCs lie. For simplicity, only one α_1 subunit is represented, since the α_2, β, γ and δ subunits have only a modulatory action on α_1. In the scheme α_1 is depicted as four repeated domains (I, II, III, IV), each containing six transmembrane segments (S1-S6). The S4 segments (yellow cylinders) of each domain contain positively charged aminoacid residues and are arranged to form the pore of the α_1 subunit. When the action potential depolarises the TT membrane the S4 charged aminoacid residues sense the voltage and move according to the new membrane potential. This 'intramembrane charge movement', ICM, determines the L-CaC opening and the movement of the loop between the II and III domain (in the scheme indicated as dotted and continuous line). As a consequence, the coupled RyR/CRC opens and the luminal Ca^{2+} stored in the SR can flow into the myoplasm (red arrows). This process is known as ECC. The conformational change of RyR/CRC in turn acts as a retrograde signal towards the L-CaC enhancing its voltage sensing function.

ICM involves three groups of charges with different voltage thresholds and voltage dependence. In fact, in normally polarized skeletal muscle fibres, ICM has been resolved into three components, an early $q_ß$, evoked by any depolarising step, and two delayed components, q_γ and q_h (Francini *et al*. 2001; Squecco *et al*. 2004) evoked only by voltage steps more positive than a certain threshold (about –56 and –38 mV in frog and rat, respectively). The time course of $q_ß$ shows a monotonic decay (Fig. 2) and it seems not to be involved in ECC since the total amount of charge moved is not affected by pharmacological interventions directed at L-CaC such as Cd^{2+}, nifedipine or alkanols. The hump–form charges q_γ and q_h can be resolved into two different ICM components by evaluating the voltage dependence of the amount of charge moved by depolarising steps above the voltage threshold (Fig. 3). In particular, the q_γ movement triggers the opening of the coupled RyR/CRC, allowing a high Ca^{2+} flux from the SR into the myoplasm and promoting muscle contraction (Fig. 2B,C red arrow through RyR/CRC). The q_h charge mobilization determines the opening of the sarcolemmal L-CaC that allows Ca^{2+} influx (I_{Ca}) from the external medium into the myoplasm (Fig. 2B,C red arrow through L-CaC). This may further enhance ECC by acting on RyR/CRC via Ca^{2+}-induced Ca^{2+} release.

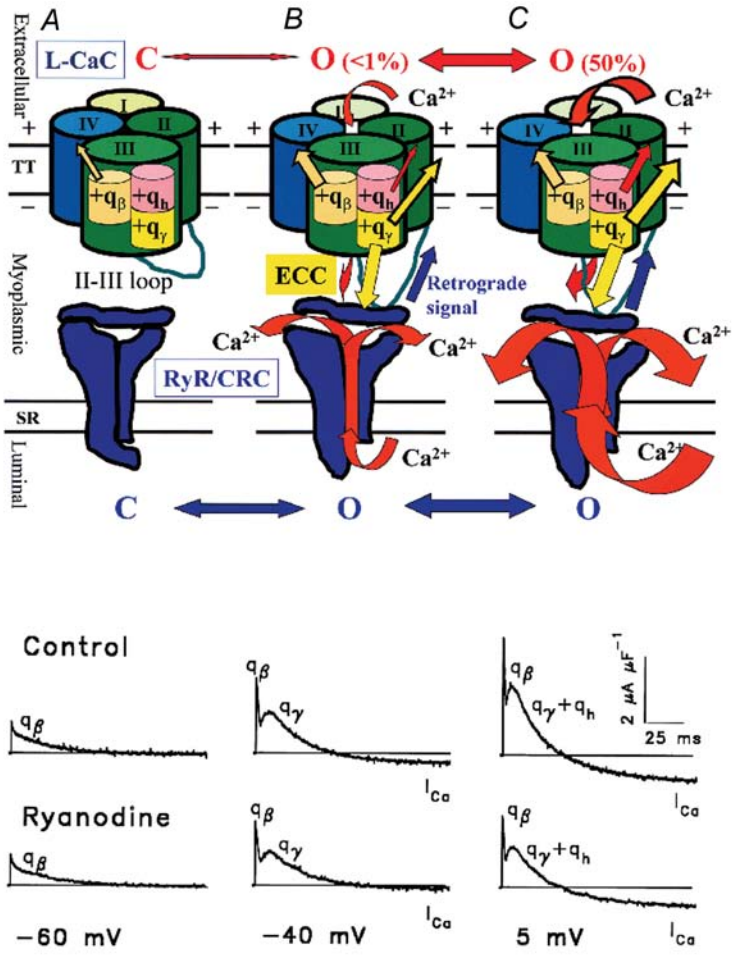

Figure 2 (left). Scheme of orthograde signal from L-CaC to RyR/CRC (ECC), and retrograde signal from RyR/CRC to L-CaC

A-C, Each panel shows the conformational state and the current recorded without and with ryanodine at -60, -40 and 5 mV, respectively. For simplicity, in the upper part of the panels the L-CaC is indicated only by the I-IV domains of one α_1 subunit and only one group of q_β, q_γ and q_h charges related to the positively charged S4-segment is depicted. The amount of charge moved is shown by the thickness of the corresponding arrow (orange for q_β, pink for q_h and yellow for q_γ). The opening state, closed (C) or open (O), of L-CaC and RyR/CRC is indicated respectively above and below each channel. At –60 mV only the charge q_β moves and both L-CaC and RyR/CRC are closed (A). Above the voltage threshold, –56 mV, also q_γ and q_h move and L-CaC opens (B and C). The mobilisation of q_γ determines the movement of the II-III loop establishing the orthograde signal, ECC, that in turn opens the RyR/CRC and causes the release of luminal Ca^{2+} from SR. The movement of q_h determines the opening of L-CaC and the influx of Ca^{2+} from the extracellular medium (I_{Ca}). This further improves the ECC since it facilitates the opening of RyR/CRC by the Ca^{2+}-induced Ca^{2+} release mechanism. Finally, the conformational change of RyR/CRC acts, in turn, as a retrograde signal towards the L-CaC, enhancing its voltage sensing function. The related current records are shown at the bottom of each panel (Control) and are evoked by 150-ms pulses at the voltage indicated in the bottom of the panels from a holding potential of –100 mV. The current traces recorded in the presence of ryanodine (Ryanodine) show that q_γ, q_h and I_{Ca} are depressed in size whereas q_β is spared. Temperature: 16°C. Fibre diameter 65 µm, linear capacitance 6.9 nF.

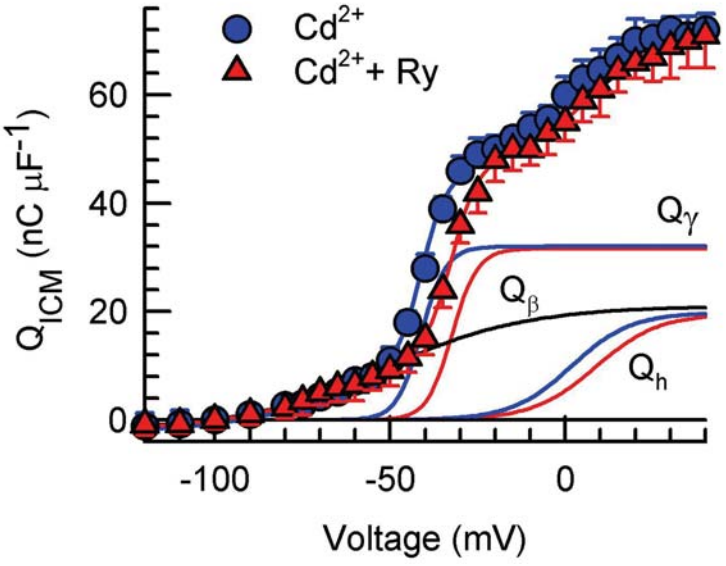

Figure 3. Ryanodine shifts towards positive potentials the voltage dependence of the steady-state amount of q_γ and q_h moved

The total amount of ICM moved, Q_{ICM}, is calculated by the time integral of the current traces recorded in Cd^{2+}-containing external solution to minimize I_{Ca}. The panel shows the Q_{ICM} versus voltage plots evaluated in fibres bathed before blue ●, and 40 min after the addition of ryanodine to this solution, red ▲, (n = 9). Lines through the data are representing the best fit as the sum of three Boltzmann functions to $Q_{ICM}(V)$ plots. For comparison, we illustrate the $Q_\beta(V)$, black line, and $Q_\gamma(V)$ and $Q_h(V)$ calculated before (blue line), and 40 min after, the addition of ryanodine (Ired line). The plots clearly show that the hump charge component moved above the voltage threshold is due to the movement of two kinds of charge (q_γ and q_h). The transition voltages at which the half amount of charge of q_β, q_γ and q_h without ryanodine moves are -51.5, -40 and 1.4 mV, respectively. Due to these different transition voltages, at -40 mV the 50% of q_γ is mobilized whereas only <1% of q_h moves; at 1.4 mV all the charge q_γ and 50% of q_h are mobilized. The maximal amount of q_β, q_γ and q_h is not affected by ryanodine treatment. The transition voltage at which the half amount of charge of q_β moves is not modified, whereas a positive voltage shift of 4-9 mV is observed for q_γ and q_h. Consequently, at -40 mV in the presence of ryanodine only about 15% of q_γ and at 1.4 mV only 30% of q_h move. Accordingly, this voltage shift is the cause of the decreased amplitude observed with ryanodine in the current traces of Fig. 2.

As described above, ECC is a one-way interaction between two proteins where the voltage-sensing promotes the RyR/CRC activation via mechanical and Ca^{2+}-dependent coupling (Fig. 2B,C yellow and red arrows, respectively). Some evidence suggests a more complex functional communication. A reciprocal interaction, or cross-talk, is possible between these two proteins that involves specific regions of the coupled RyR/CRC. Thus, in addition to 'receiving' the orthograde ECC signal from the L-CaC, RyR/CRC seems to 'answer' with a retrograde regulation (Fig. 2B,C, blue arrow) that increases the Ca^{2+} channel activity of the L-CaC (Nakai *et al.* 1998) causing an enhancement of I_{Ca}.

A point that needs clarification is a discrepancy in the literature whereby Csernoch *et al.* (1991) and García *et al.* (1991) report that similar manipulations to those used in Squecco *et al.* (2004) do not influence I_{Ca}, whereas Nakai *et al.* (1998) report that they do observe a retrograde regulation of I_{Ca} by the RyR. The idea to be considered is that manipulations of the RyR should reciprocally influence the behaviour of any charge components with which it makes allosteric contact (García *et al.* 1991; Csernoch *et al.* 1991; Jong *et al.* 1995; Huang, 1996; Chawla *et al.* 2002) and should spare only charge components that are not supposed to originate in the L-CaC and/or that are hardly involved in ECC.

In this debate, it appeared interesting to clarify the effects of the retrograde signal on I_{Ca} and which charge components are involved in the cross-talk between the L-CaC and RyR/CRC.

To this end, Squecco *et al.* (2004) did experiments in single fibres dissected from the semitendinosus muscle of the frog in voltage-clamp condition using the double-Vaseline-gap method (Francini *et al.* 2001). A number of pharmacological interventions were carried out that sought to interfere with a) L-CaC, by using channel blockers such as Cd^{2+} (Francini *et al.* 2001), nifedipine and 1-alkanols (heptanol and octanol), and b) RyR/CRC, by using specific blockers such as ryanodine

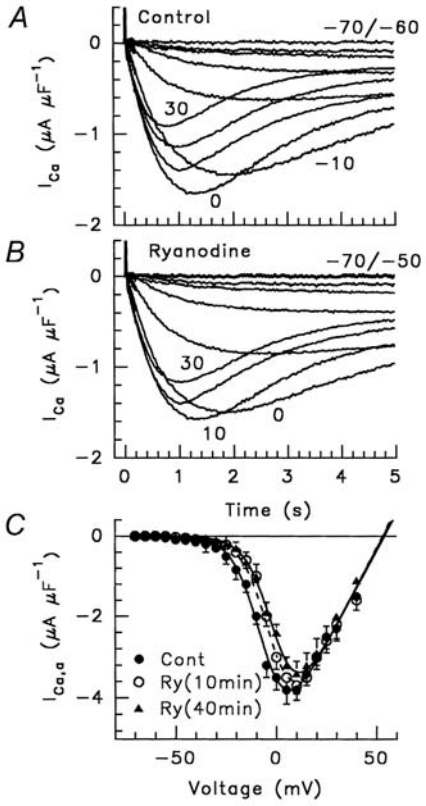

Figure 4. Ryanodine blocks RyR/CRC and shifts the transition voltages of I_{Ca} towards positive potentials
Current traces obtained through the imposition of long depolarising test pulses (5 s) from a holding potential of –100 mV. Test voltage pulses ranged from –70 to 30 mV in 5-mV increments. For clarity only the traces from –70 to 30 mV in steps of 10 mV are shown. Some potentials are indicated in mV next to the traces. *A*, typical experiment performed in a fibre bathed in control external solution without Cd^{2+} to observe I_{Ca}. *B*, the experiment was performed in the same fibre 40 min after the addition of 100 μM ryanodine to this solution. *C*, I_{Ca} peak size plotted versus voltage. A voltage shift of 7 and 10 mV towards positive potential of the voltage threshold of I_{Ca} appearance and of its transition voltage can be observed 10, Ry (10 min), or 40 min, Ry (40 min), after the addition of ryanodine (n = 6).

(Garcia *et al.* 1991) and ruthenium red (RR) (Csernoch *et al.* 1991), known to suppress Ca^{2+} release from RyR/CRC.

We found that nifedipine reduced the amount of q_γ and q_h moved by ~90 % and ~55 % respectively, whereas 1-alkanols completely abolished them. Both interventions spared q_β. Ryanodine and RR did not affect the amount of q_γ and q_h moved, but shifted their voltage dependence (Fig. 3) and that of I_{Ca} activation more positively by ~4-9 mV (Fig. 4); conversely, Ryanodine and RR spared q_β. The effect of ryanodine together with those of nifedipine and 1-alkanols, demonstrate that q_γ and q_h both reside in the DHPR/L-CaC and represent separate independent processes from q_β. The parallel voltage dependence of q_h and I_{Ca} is in agreement with the hypothesis that q_h is the sensor for the L-CaC opening and that q_γ is the sensor for ECC. Moreover, our results demonstrate that, in the absence of RyR/CRC blockers, the opening of the RyR/CRC facilitates q_γ and q_h movement as well as the opening of L-CaC by a retrograde signal.

We thus confirm earlier reports that manipulations of the RyR/CRC reciprocally influence the q_γ charge (Huang, 1996) and I_{Ca} (Nakai *et al.* 1998) and we report the novel finding that q_h is influenced as well. Taken together, the above observations have deepened our understanding of the cross-talk hypothesis between the L-CaC and RyR/CRC, clearly suggesting that a kind of retrograde regulation by RyR/CRC facilitates the movement of the q_γ and q_h charge and the opening of L-CaC and, in turn, the ECC process.

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Tremor

Bettina Pollok and colleagues consider what is physiological in pathological tremor. As with much else, networks are the key

Since the pioneering neuroanatomical studies of Paul Broca (1824-1880) and Carl Wernicke (1833-1904), it is generally accepted that different brain areas are associated with specific functions. However, functional neuroimaging techniques demonstrate that even the execution of apparently simple tasks is associated with neural activity in a widely distributed cerebral network comprising cortical as well as subcortical structures. Although these studies associate certain tasks with activation of specific brain structures, it remains unclear how information is interchanged between these areas.

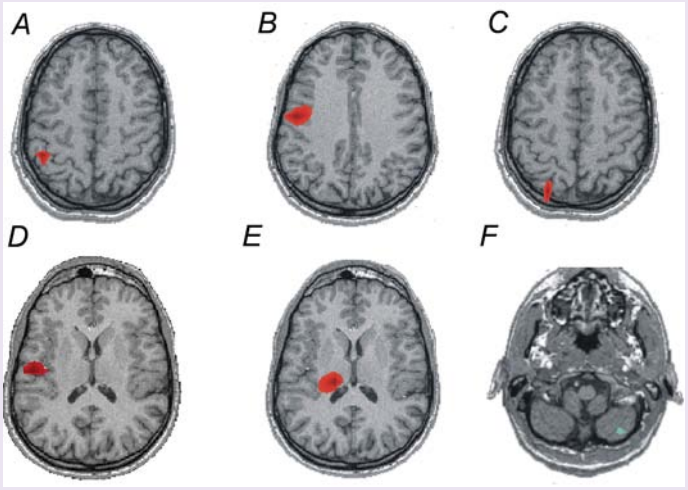

Figure 1. Localizations of coherent activity in one representative subject imitating the typical antagonistic PD resting tremor. Synchronized oscillatory activity was detected in the contralateral primary sensorimotor cortex (*A*), the premotor cortex (*B*), the posterior parietal cortex (*C*), the secondary somatosensory cortex (*D*), the thalamus (*E*) and the ipsilateral cerebellum (*F*).

There is growing evidence that synchronization of oscillatory neural activity might be a fundamental mechanism of information coding in the brain (Singer, 1999). Coherence and phase synchronization are established measures for quantifying coupling between different brain sites. Recent studies substantiate the hypothesis that relevant information in the brain is coded by accurate timing of neuronal discharges in large scale networks. Such synchrony between spatially distributed neural activity can be investigated non-invasively by using magnetoencephalography (MEG) together with a recently developed analysis tool *Dynamic Imaging of Coherent Sources* (DICS; Gross *et al.* 2001). MEG allows for the investigation of brain activity in the range of milliseconds, which is a fundamental premise for characterizing synchronized oscillatory activity. Additionally, DICS provides a topographic map of coherence between different brain sites associated with the execution of a specific task or with a specific motor behaviour. Thus, MEG data provide information about brain structures involved in a task and – most importantly – about functional interactions between these areas. Since it has been argued that relevant information in the brain may be coded by changes in the dynamic interplay between different structures without changes of the local activity, investigation of the dynamic interaction between neural assemblies reveals new insights into the understanding of how information is processed in the brain.

In our recent work we have focused on the investigation of synchronized oscillatory activity associated with pathological as well as physiological motor behaviour. Tremor is defined as an involuntary oscillating movement of a body part, most frequently the upper extremities. It can be observed as a physiological phenomenon in healthy volunteers and as a pathological symptom associated with a wide variety of movement disorders. As early as 1886 Horsley and Schafer speculated that tremor might have - at least in part - a neurogenic basis (Horsley & Schafer, 1886). In a recent study it has been demonstrated that resting tremor in Parkinson's disease (PD) is associated with a cerebello-diencephalic-cortical network oscillating at tremor as well as at double tremor frequency (Timmermann *et al.* 2003). These data agree well with the assumption that central mechanisms play a crucial role in the origin of tremor. However, the results raise the question about the specific pathological nature of the demonstrated network: does it reflect a pathological phenomenon *per se*, or does it represent a functional network underlying physiological motor behaviour, which may be specifically altered in PD resulting in resting tremor?

To answer this question we investigated cerebro-cerebral coupling in a group of healthy subjects voluntarily imitating the typical antagonistic resting tremor (Pollok et al. 2004). Our results demonstrate that, indeed, the same oscillatory network subserves voluntary tremor as well as involuntary resting tremor. Our data, therefore, indicate that coupling within cerebral networks represents a fundamental characteristic of motor control, and that pathological movements like PD tremor may be due to alterations within such physiologically pre-existing networks. Figure 1 summarizes the localization of coherent activity in one representative subject imitating the typical antagonistic PD tremor.

The constituents of the oscillatory network of pathological PD and voluntary tremor are the same.

However, we found important differences when comparing coupling strength within this network between PD patients and healthy subjects imitating resting tremor. First, significant coupling between the diencephalic structure and the primary sensorimotor cortex was reduced in the healthy controls as compared to the PD patient group. This implies a stronger influence of the thalamus on the

activity of the primary motor cortex in PD patients. Second, coupling between the premotor cortex and the primary sensorimotor cortex was enhanced in the healthy group most likely indicating that the premotor cortex drives M1 resulting in the voluntary 3-6 Hz tremor. In contrast, in the patient group M1 might be driven by deep diencephalic structures like the thalamus, resulting in involuntary tremor.

Although one has to be cautious when comparing data from patients with those from healthy subjects, since subjects and patients were not age-matched, our data substantiate the hypothesis that PD tremor is based on a physiological oscillatory network, and that characteristic alterations within this network are most likely associated with the generation of tremor.

To summarize, the investigation of oscillatory interactions between brain sites involved in a specific task provides physiologically and pathologically important insights into the functional connectivity between brain areas. The comparison between healthy subjects imitating tremor and PD patients clearly demonstrates that it is not necessarily the local activity of brain areas, but rather the dynamic interplay between these structures, which might be crucial for the understanding of physiological and pathological motor behaviour.

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Channel gating in the LGIC receptor superfamily – insights into the signal

Recent papers on ligand-gated ion channels reveal more molecular detail on the conformational changes that follow ligand binding and lead to pore opening

Clockwise from top left: Nathan Absalom, Trevor Lewis Peter Schofield

Understanding receptor function has proved to be a demanding task. Once ligand-gated ion channel (LGIC) receptors were identified as the engines that converted chemical signals into electrical currents at the synapse, the structure of these molecules and how this related to their function became a major topic of fundamental research. Recent advances have led to an unprecedented level of detailed knowledge of the structure of the nicotinic acetylcholine receptor (nAChR). By homology, this structural information has been applied to other members of the cys-loop family of receptors – the glycine, γ-aminobutyric acid type A ($GABA_A$) and serotonin type III ($5\text{-}HT_3$) receptors. These receptors are all pentameric complexes with each subunit sharing a common topology of a large extracellular N-terminal domain and four transmembrane domains (M1-M4), of which the M2 lines the channel pore. The merging of molecular structure information and traditional mutational and functional analysis has seen the field leap ahead in our understanding of these receptors.

The recent advances in the field have been driven by two important publications. The first was the structure of the acetylcholine binding protein (AChBP) derived from X-ray crystallography (Brejc *et al*. 2001). The AChBP scavenges acetylcholine molecules at cholinergic synapses in

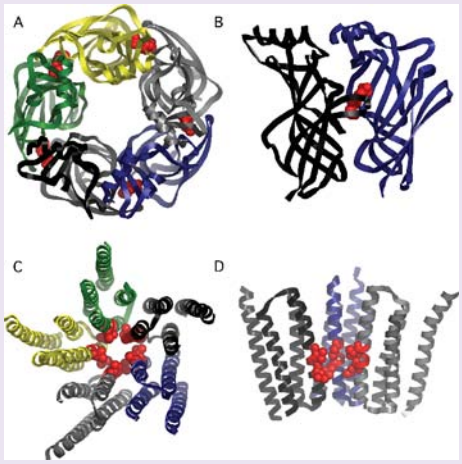

Figure 1. *A* shows a ribbon diagram of the top view of the AChBP as described by Brejc *et al.* (2001). A HEPES molecule located in the ligand-binding pocket is shown in red between adjacent subunits. The five subunits are coloured differently. *B* shows a view of the ligand-binding pocket between two adjacent subunits from the exterior of the AChBP. *C* shows a ribbon diagram of the top view of the pentameric arrangement of the transmembrane domain of the nAChR. The α-subunits are coloured in black and yellow, the β-subunit is coloured in blue, the δ-subunit is coloured in grey and the γ-subunit is coloured in green. Residues that physically block ion flow are coloured red and depicted as spheres. *D* shows a ribbon diagram of three subunits (α, β and δ) in a side view of the nAChR transmembrane segment to show a cross-section of the channel pore. The residues within the hydrophobic girdle that prevents ion flow in the closed state are represented in red.

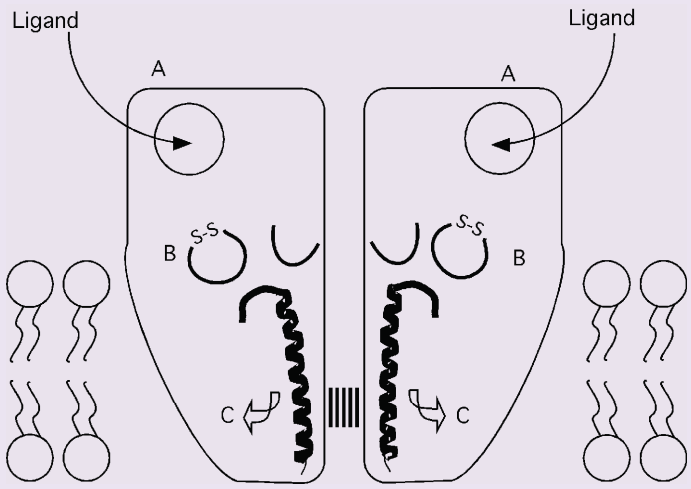

Figure 2. A proposed model for the gating mechanism of LGIC receptors. Upon ligand binding (*A*), there is a conformational change that results in a 15-16° rotation of the extracellular domain. This rotation is thought to result in loop 2 and loop 7 rotating near the M2-M3 linker (*B*). This movement is thought to cause the M2-M3 loop to change conformation, leading to the rotation of the pore region (*C*). This breaks the hydrophobic girdle, depicted by black bars, created by the central leucine residue and allows ions to pass through.

the snail *Lymnaea stagnalis* and has a high degree of similarity in amino acid sequence to the extracellular domain of the nAChR (Fig. 1*A,B*). This gave researchers a three-dimensional portrait of the molecular structure of the ligand-binding pocket. Homology structures were built for the extracellular domains of the acetylcholine receptor and the other members of the cys-loop family of receptors to help investigate other questions of receptor function. Of particular interest was the location of the conserved cys-loop and loop 2 of the extracellular domain, which appeared to be in position to interact with the transmembrane domains of the receptor complex.

Using traditional site-directed mutagenesis and electrophysiological techniques, electrostatic interactions were found between a lysine residue in the M2-M3 linker region and acidic residues in the cys-loop and loop 2 that were critical for coupling agonist binding to channel gating in the $GABA_A$ receptor (Kash *et al*. 2003). The homologous structures in the glycine receptor were also found to be critical in this signal transduction process, although the electrostatic interactions were not the same (Absalom *et al*. 2003). This is thought to be a consequence of different protein sequences in these regions.

The second key publication describes the refined electron micrograph derived structure of the *Torpedo* AChR, which provides a detailed three-dimensional structure of the transmembrane domains and, in particular, the channel pore (Miyazawa *et al*. 2003) (Fig. 1*C,D*). The pore structure indicates that there is a 'hydrophobic girdle' formed by conserved residues located in the middle of the M2 domain that constitutes the channel 'gate', blocking ion flow in the closed state. Rotation of one or two of the M2 domains would disrupt the hydrophobic interactions with adjacent helices and collapse the hydrophobic girdle, allowing ions to flow through the channel.

From earlier electron density structures of the AChR, it was known that binding of agonist causes rotations in the extracellular domain of the receptor and of the M2 domains (Unwin *et al*. 2002), but how these events were coupled was not clear. That these conformational events were coupled sequentially to open the channel pore had been demonstrated by Grosman and colleagues (2000). They mapped a 'conformational wave' that propagated from the ligand binding site to the channel pore via the M2-M3 linker, as determined by linear free energy relationships. With the refined structure of the nAChR, a molecular framework is provided for these conformational changes which predicts interactions between the conserved cys-loop and the M2-M3 linker (Fig. 2). However, unlike the electrostatic interactions in the $GABA_A$ receptor, these interactions are predicted to be hydrophobic in nature in the AChR (Miyazawa *et al*. 2003).

These key publications on the structure of the AChBP and the transmembrane domain of the AChR have provided alluring details of these domains in cys-loop family of LGICs and of the possible interactions at the interface between these domains. Combined with previous information obtained by site-directed mutatgenesis studies, this has resulted in fledgling mechanism that for the first time makes specific structural links between the ligand binding domain and the opening of the channel pore (Fig. 2). There is still a lot of detail to fill in with this mechanism, but it has already identified the important elements of this process.

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Quality control

It had to happen. Research funders now need to be assured that the correct systems for quality monitoring are in place in laboratories before they sign contracts and award grants

There have been just too many occasions recently where the public has demanded to know how they can trust results. Regrettably, peer review prior to publication is not sufficient for many 'experiments' of interest, and is still not clearly relevant to the general traveller on the Clapham omnibus.

The BSE cow/sheep brain mix up was the straw that broke the camel's back (to mix a metaphor), but there have been court cases that collapsed because the scientific evidence was not robust enough, genetic tests recalled because of lack of confidence in the results, food scares such as plasticisers in baby foods that weren't, and toxins in cockles that may not have been there after all.

The announcement earlier this year regarding conditions for the award of research funding (grants, contracts, etc.) from BBSRC, DEFRA, NERC and FSA includes the following:

- managers have a responsibility to ensure a climate of good scientific practice;
- project plans must be developed in collaboration with the funding body, including risk assessment;
- the organisation must have processes in place to assure the quality of research;
- all samples and experimental materials must be comprehensively labelled and tracked;
- all research procedures and methods must be documented;
- the project leader must regularly review the records of each scientist.

Individually, some of the above are not too onerous and are probably already in place, but collectively they have the potential to increase bureaucracy considerably and place pressure on the project leader.

The funding bodies maintain that researchers have been given ample opportunity to air their grievances. The head of the UK Deans of Science Committee says that most universities remain completely unaware of the code and the deadline for complying with it!

At present neither MRC nor Wellcome Trust has yet made such a policy, but both organisations have fairly new Chief Executives. Watch this space.

It is unlikely that many potential recipients of Research Funding Body largesse have viewed the news with delight.

We all know that 'good laboratory practice', adherence to HSE codes, etc. does not guarantee the absence of mistakes. However, the climate of opinion has shifted such that the absence of relevant controls lays the research funder open to severe criticism should things go awry.

We therefore need to find a way forward that does not involve overworked scientists drowning in yet more (electronic) form filling.

There are two separate components to this. The first involves systems for laboratory practices such as ISO 9000 and its congeners. The second relates to the personnel rather than the methods. The usual approach to this (as used by the medical profession, lawyers, engineers and accountants) is a verifiable programme of Professional Development leading to Chartered status (or inclusion on the Medical Register). All worthy scientists are certain to be doing CPD anyway, and so what is required is appropriate external validation, with the lowest level of intrusion into the working life of the individual. Such a scheme needs to be flexible enough to meet the varying needs of biologists who may be working with dangerous pathogens (whether HIV, foot and mouth, or aspergillus), or assaying metabolites, monitoring cod populations, following butterfly migration, or even teaching (whether in school, higher or tertiary education) the results of such work.

The Institute of Biology (which was granted its Royal Charter 25 years ago) has been working with all these various aspects of the profession during the last few years to develop such a CPD scheme. It has now been adopted by the Defence Science and Technology Laboratory as its preferred scheme for its increasing number of biological scientists. Discussions with both DEFRA and the DTI are under way, and have been initiated with the FSA.

A pilot scheme to test CPD among more than 50 scientists from differing walks of life has been carried out, and the collected experience and wisdom is now incorporated into the final scheme.

The official launch is scheduled for January 2005.

Further information can be found on the IOB website: *http://www.iob.org*

Georgina Day
Education Officer
Alan D B Malcolm
Chief Executive
Institute of Biology, Queensbury Place, London, UK

Pfizer and Blue Band Prize winners

Abigail Woodfin (King's College, London) was awarded a Pfizer Prize for her oral communication at the Cambridge Meeting in December, 2003. She will receive her award at the King's College London Meeting in December.

At the Glasgow Meeting in March, Jeng-Haur Chen (University of Bristol) and Tahl Holtzman (University of Cambridge) were awarded Pfizer Prizes for their oral communications and Valerie Collins (University of Leeds) won a Blue Riband Prize for her poster communication

Congratulations to all four.

FENS goes from strength to strength...

This year's Lisbon meeting convinces Thelma Lovick that the Federation of European Neuroscience Societies is firmly established on the scientific map

In the mid 1990s the European Neuroscience Association was languishing. With a dwindling number of participants attracted to its meetings, the ENA was in danger of becoming moribund. Then, in the manner of many a fading pop star, it underwent a makeover and re-invented and re-launched itself as FENS: the Federation of European Neuroscience Societies. On alternate years, the national neuroscience societies from the member countries agreed to waive their annual meetings in favour of a large European meeting. In 1998 a phoenix rose from the ashes of the ENA in the form of the first FENS Forum, which was held in Berlin. The Berlin meeting proved popular and has been followed by successful meetings with increasing numbers of participants in Brighton, Paris and, this year, Lisbon. FENS is now firmly established on the scientific map.

Portugal was still reeling from the ravages of the soccer World Cup when the neuroscientists arrived, with a few forlorn flags still fluttering from cars and buildings. But the rarified atmosphere of neuroscience left all that behind. This was a well organised meeting, held at a conference centre that was easily accessible from city centre hotels and, importantly, was large enough to hold the nearly 5,000 strong cohort of registrants without too much of a crush. It was a noticeably 'young' meeting. More than 40% of the participants were postgraduate students, many helped by generous bursaries from FENS itself or IBRO or the various national neuroscience societies. And they were not disappointed. The science was wide-ranging with excellent plenary speakers, up-to-date symposia and lively poster sessions that changed twice daily.

Perhaps an index of the success of a meeting can be gauged from the last day. In Lisbon, the final poster session, considered by many to be the graveyard slot, was well-attended. Moreover the closing plenary lecture was a real treat. It says something for the confidence of the organising committee that they had booked a large lecture theatre. Their optimism was vindicated by the excellent turnout and the audience was rewarded by a really exciting presentation by Miguel Nicolelis from Duke University, Durham, USA who reviewed his recent advances in using real-time computational models to investigate how ensembles of neurones encode motor information in the primate. This was real cutting-edge stuff that provided a glimpse into a not-so-far-off world in which brain-machine interfaces will be used to power neuroprosthetic devices that will revolutionise the lives of amputees and victims of traumatic brain injuries.

The soul of Lisbon – a fado singer in the Bairro Alto gives it her all

Can FEPS follow suit?

The Federation of European Physiological Societies (FEPS) is in a similar position to the old ENA of 10 years ago. However, things are set to change. Next year sees the introduction of FEPS meetings to be held in conjunction with a meeting of one of its constituent members, as part of their calendar of meetings. The venue for the first joint venture is Bristol in July, 2005 where FEPS will hold a joint meeting with the Physiological Society. Based on the experience of FENS, this format should be a success. Indeed, interest in the meeting is already running high, with some 40 proposals submitted for the 15 scheduled symposia slots. In addition, there will be prize lectures, workshops and poster sessions spread over 4 days. As a further attraction, the meeting will be preceded by an international meeting on the mammalian myocardium and followed by another on chloride channels. So make a note in your diary for Bristol next July!

Thelma Lovick
Department of Physiology, University of Birmingham

Further details of the Physiological Society/FEPS meeting will be posted on the Society's website: *www.physoc.org*

Why waste scarce grant money on a hotel? A neuroscientist awakes after a night under the stars in Lisbon

Society for Free Radical Research International

The XII Biennial Meeting of the SFRRI was held in Buenos Aires, Argentina from 5-9 May, 2004 at the invitation of Alberto Boveris and Cesar Fraga

At this meeting the Physiological Society sponsored a research symposium entitled *'Phytoestrogens and Flavonoids: Cell Signalling and Physiological Action*', which was co-organised by Jose Viña (Universidad de Valenica, Spain) and Giovanni Mann (King's College London). The speakers included Jose Viña, Giovanni Mann, Cesar Fraga (University of Buenos Aires, Argentina) and Augustin Scalbert (INRA, Saint-Genes-Champanelle, France), who highlighted novel roles for phytoestrogens in regulating intracellular signalling pathways involved in antioxidant gene expression, endothelial nitric oxide production and control of blood pressure. Our symposium integrated well with another symposium on the antioxidant properties of flavonoids, which was co-ordinated by Frederico Leighton from the Catholic University of Chile, Santiago, Chile. Invited speakers and younger scientists attending our symposium adjourned to a symposium dinner, sampling Argentine beef and enjoying a sensational tango evening!

Above: Symposium co-organisers (Giovanni Mann and Jose Viña) with Consuelo Borras, an affiliate of the Physiological Society, at the Iguazu Falls. From its source in the Serra do Mar, not far from the Atlantic coast, the Rio Iguazu (or Iguassu) flows westward for about 820 miles across southern Brazil. The river grows steadily in volume as it meanders across the uplands of the Parana Plateau. The river takes its grandest leap just a short distance above its confluence with the Parana, where the Iguazu forms a boundary between Argentina and Brazil. The thunderous roaring of the water can be heard from miles away (http://www.argentour.com/iguazui.html).
Below: Dinner with young participants from the UK, Spain, New Zealand and China

The total number of registered participants at the SFRRI meeting was 436, including 79 invited speakers, 213 students (undergraduate, graduate, and postdoctoral), with 17 participants from the UK. There were five plenary lectures, 135 oral presentations in 24 themed symposia; 307 poster presentations in 19 themed sessions and 16 clinical presentations in three clinical workshops. The programme and abstracts were published in *Free Radical Biology and Medicine* **36,** Supplement 1 (ISSN 0891-5849).

In order to encourage the scientific careers of PhD students and postdoctoral fellows in the field of free radical research, the meeting organisers also scheduled a 'free radical school' and several Young Investigator Colloquia (similar to our Young Physiologists' Symposia). The 'free radical school' met early each morning with established researchers discussing the following topics: basics and chemistry of free radicals; antioxidants versus pro-oxidants; thiol systems; Nox enzymes: where, when and why; markers of oxidative and nitrosative stress; flavonoids: new ways of thinking in nutrition; free radical hypothesis of aging; and the role of nitric oxide in atherosclerosis.

The main support for the meeting in Buenos Aires was provided by the SFRRI and the Society for Free Radical Biology and Medicine. Symposia and travel awards for younger scientists were also sponsored by the International Union of Biochemistry & Molecular Biology, National Council for Scientific Research of Argentina, the Physiological Society, American Physiological Society, Molecular & Cell Biology Network, Linus Pauling Institute, and the Center for Free Radical Biology at the University of Alabama, Birmingham, USA.

We thank the Physiological Society for sponsoring the symposium and feel that this venue provided a basis for exploring closer links between our Society and the SFRRI. After discussion with members of the SFRRI Council in Buenos Aires, we hope to hold a Young Physiologists' ('Researchers') Symposium at the forthcoming meeting of the Society for Free Radical Research (Europe) in Leicester from 8-11 July, 2005. This will enable affiliates from our Society, SFRRI and, potentially, the Biochemical Society to meet and discuss their work in the field of free radical research.

Jose Viña
Universidad de Valencia, Spain
Giovanni Mann
King's College London, UK

An education in biomedical *in vivo* research

Thomas Solomon and Shokufeh Tavassoli report on the integrative physiology/pharmacology course at the University of Bristol in June

The integrative physiology-pharmacology course began on 28 June, 2004, jointly sponsored by the Physiological Society and the British Pharmacological Society, and further supported by Pfizer, Eli Lilly, Merck Sharp & Dohme, GlaxoSmithKline, and the Wellcome Trust. Hosted by the Department of Physiology at the University of Bristol, the week was to prove quite challenging for the participants, giving us a great insight into the principles of experimentation on animal models in *in vivo* research as well as an in-depth understanding of the ethics behind using such animals: the 'three R's', *refinement, reduction, replacement,* will never be forgotten.

Students from varied backgrounds, ranging from postgraduate exercise biochemists to undergraduate pharmacologists, now have a greater understanding of the methods employed in physiological and pharmacological research to help them make informed decisions about their future careers

The purpose of the week was to build on the theory taught at the Home Office Personal Licence training course held earlier in the year. It was a joint academic-industry venture providing young inexperienced scientists with an education in *in vivo* research methods applied to mammalian systems, with the aim of encouraging successful careers in postgraduate study or postdoc and industrial research. Selected from students all over the UK and Ireland, the participants were from varied backgrounds ranging from postgraduate exercise biochemists to undergraduate pharmacologists, and this was to become clearer as different people's strengths were called upon over the week.

It all seemed like a huge shock on the first morning trekking up the mountainous Park Street to breakfast and to our first lectures, but from the word go we were learning of the principles of pain assessment, analgesia, and anaesthesia. The first practical run by Sally Lawson gave us each a chance to try a tracheal or blood vessel cannulation on a rodent, whilst monitoring its signs of vitality and maintaining its body temperature – challenging work but amazingly successful. The first day was exhausting, but the local Weatherspoons revived us, as did the interestingly flamboyant Pineapple Club next door to our residence!

As the week progressed, we all learnt a vast amount from some great lectures by Bruce Matthews on neural recording and stimulation techniques, and some interesting practicals from Lucy Donaldson and Stephen Lisney studying nociceptive responses and C-fibre innervation. With help from Roger Francis and Joe Roe, we also had the chance to practice our animal handling techniques. The experiments included: investigating autonomic agonists and antagonists on respiratory rates and blood pressure recordings (Max Headley), recording spinal reflex responses to mechanical and electrical stimulation (Bridget Lumb), and recording blood pressure using the radio-telemetry technique (Julian Paton and Hidefumi Waki). We were even lucky enough to have John Parrot, the head of non-clinical statistics at Pfizer (one of the companies sponsoring the course), give us seminars on statistical data analysis. All the concepts were completely foreign to us all but were taught very well by the staff at Bristol.

On Thursday, we learnt about the cerebellum and its role in movement control from Richard Apps and his group. Having covered the basic principles as part of our undergraduate teaching, it was a great opportunity to further our understanding. From previous lectures, we knew that Purkinje cells receive their input either indirectly from mossy fibres, or directly from the climbing fibres and how these lead to differences in spike activity. It was particularly interesting to use this knowledge in a practical context and to see the time scale involved in obtaining the data. After a lot of patience and determination, it was quite exciting to see the simple and complex spikes on the computer screen. It showed us just how patient and careful one must be – something we all take for granted when reading textbooks!

On the penultimate night the course tutors hosted a social at a local Thai restaurant. It was a nice opportunity to chat to them and to learn more about their individual areas of research, and of course to dance – the opinion being 'no one will see us again'! One of our colleagues even decided to introduce the Bristolian public to his very own

'call of Gondor'. It was a lovely evening, and a great way to finish the week. The only problem was our early start and final assessment exam the next day!

At the start of the week, when we were given our course handbooks, we could not believe the number of things that had been planned. It seemed impossible to learn so much in just 5 days! In all, it was a great chance to carry out experiments and techniques we might not otherwise have had. We now have a greater understanding of the methods employed in physiological and pharmacological research, and this knowledge will help us make an informed decision about our future careers. We are sure the course organisers will deem it a success, and that the sponsors will be happy to have funded such a course to educate future scientists. We would like to thank Richard Apps and all the staff at Bristol for organising this great opportunity, and the industries that sponsored the course, who we are sure will benefit greatly from this in the years to come. This has been a hugely worthwhile experience for everyone involved and we wish every success to next year's education in *in vivo* methods course.

[1]Thomas Solomon
[2]Shokufeh Tavassoli

[1]Human Performance Laboratory, University of Birmingham
[2]Department of Physiology, University of Bristol

Delegates at the Alternative Muscle Club conference enjoyed the informal, non-hierarchical environment to discuss their work and seek feedback

Alternative Muscle Club

The 23rd Annual Conference took place from 25-27 July at Imperial College, London

It could be argued that 1981 was a seminal year in muscle research, not because it was the year of my birth, but because it saw the inception of the Alternative Muscle Club conference.

Since the inaugural meeting the mantle of hosting this annual event has fallen to universities across the country. Early gatherings were a somewhat unshaven affair of young, savoir-faire scientists giving *ad hoc* presentations before retiring at night to the floors and sofas of their hosts' digs. In recent years things have progressed – we now have beds, for example – but the essence of the meeting remains unchanged: to provide a supportive, informal and friendly platform for young (in terms of career, not age) scientists to discuss their work and seek feedback, all without the pressures of supervisors and the like being present. So it was with glee that our committee, formed from Imperial's and KCL's finest, organised and hosted the 23rd annual AMC conference at Imperial College London.

The conference took place over two and half days and, while there were ample presentations on muscle structure, function and disease, there were also contributions from non-muscle myosin fields. The presentations from 15 delegates, out of 30 who attended, were grouped into six sessions: non-muscle motor proteins; physiology and disease; sarcomere structure and function; X-ray diffraction and FLIM; disease and dysfunction; and macromolecular crystallography.

During the disease and dysfunction session, Chi-Ying Li (Institute of Urology and Nephrology, UCL) gave the provocative, but clinically entitled talk *Contractile activation of corpus cavernosal tissue*, for which she later received the award for best oral presentation. The majority of delegates presented posters, with viewing time allotted each day between sessions. Four invited guest speakers gave plenary lectures, each relevant to a specific session. They were: John Kendrick-Jones (myosin VI function), John Squire (sarcomere structure), Malcolm Irving (X-ray diffraction studies of muscle fibres) and Anne Houdusse (X-ray crystallography and muscle function).

The format of the AMC is, as the name suggests, alternative and it is this unorthodox nature that is fundamental to its value. The non-hierarchical environment was witnessed by the fervent discussion in the display room and after talks. Additionally, there was ample scope for meeting others working in related fields and the opportunity for collaborations. A successful meeting ended with the responsibility for AMC 2005 being passed to Paul Robinson of Oxford University.

Verl Siththanandan
Committee Treasurer
Imperial College London, UK

The Journal of Physiology

New Editors

Eight new Editors were recently appointed to the Editorial Board of *The Journal of Physiology* – Ann Bonham, Roberto Bottinelli, Leonardo Cohen, Michael Evans, James Jones, Haruo Kasai, Yoshihiro Kubo and Eduardo Ríos.

Ann Bonham is Professor and Chair of Pharmacology and Professor of Internal Medicine in the School of Medicine at the University of California, Davis. She was awarded her PhD from the University of Iowa in 1986, where she worked with, and was inspired by, the late Mike Brody.

Ann's research interest is in central neural regulation of the cardiovascular and respiratory systems. Cardio-vascular homeostasis is regulated, in part, by neuronal signalling through oligosynaptic pathways in the brainstem. The synaptic and intrinsic electrical properties of the neurons in these brainstem pathways combine to generate an appropriate neuronal output to regulate blood pressure and heart rate. By combining whole cell patch clamping, microinjections of neuroactive agents in the brainstem of conscious animals, and molecular biological approaches, the laboratory seeks to understand how these neurons are regulated under normal conditions and how changes in their synaptic and intrinsic properties induced by exercise, cardiovascular disease or exposure to air pollutants modify neural regulation of cardiovascular homeostasis.

A second related research interest is aimed at neural regulation of respiration, cough and lung function. The laboratory studies how exposure to air pollutants including ozone, allergen, and second hand smoke triggers synaptic and intrinsic changes in brainstem neurons regulating cough and lung function through CNS reflex pathways. Using electrophysiological and molecular biological approaches, it is hoped to understand how the changes in the phenotype and behaviour of these neurons trigger increases in cough and changes in breathing pattern in response to environmental stimuli.

Roberto Bottinelli received his MD in 1981 and his PhD in physiology in 1989 from the University of Pavia, Italy. From 1982-1983 he worked at the University of Washington in Seattle and from 1986-1987 at the University of St Andrews, Scotland, and thereafter collaborated with several foreign laboratories. He is currently Professor of Physiology in the Medical School at the University of Pavia. His research is mainly devoted to muscle physiology, particularly the cellular and molecular mechanisms underlying the very large structural and functional heterogeneity and plasticity of skeletal muscle in health (ageing, disuse, exercise training) and disease (muscular dystrophy and respiratory diseases). Since 2000 he has been responsible for the laboratory of muscle biophysics in the Department of Experimental Medicine of the University of Pavia that was set up by Carlo Reggiani. He is also director of the Specialization School in Sport Medicine of the Faculty.

Leonardo Cohen received his MD from the University of Buenos Aires. He was based at Georgetown University for his neurology residency, and received postdoctoral training in clinical neurophysiology at the Department of Neurology, University of California (Irvine) and in motor control and movement disorders at the Human Motor Control Section, NINDS. In 1998 he became chief of the Human Cortical Physiology Section, NINDS. He received the prestigious Humboldt award (1999) from the Republic of Germany and is an elected member of the American Neurological Association. Leonardo's lab is interested in the mechanisms underlying plastic changes in the human central nervous system and in the development of novel therapeutic approaches for recovery of function based on the understanding of these mechanisms.

Above: Ann Bonham (top), Roberto Bottinelli (centre) and Leonardo Cohen

Below:: Michael Evans (top), James Jones (centre) and Haruo Kasai

Michael Evans is a lecturer in the MacKay Institute of Communication and Neuroscience, part of the School of Life Sciences at Keele University. In 1979 he graduated from (as it was then) Queen Elizabeth College, London with a BSc in physiology. After a brief period as a Lung Function Technician at St Thomas' Hospital Department of Medicine, he started a PhD in physiology at the University of Bristol under the supervision of Roger Thomas. His project was to investigate the stoichiometry of the pH-regulating transporter in snail neurones by measuring intracellular ion concentrations using ion-sensitive microelectrodes. He graduated in 1983.

He then undertook a series of postdoctoral positions starting with a Royal Society European Exchange Programme Fellowship to work in Philippe Ascher's lab at the Ecole Normale Superieure, Paris, where he learnt how to record from single cells, and single ion channels, using the patch clamp technique. While in Paris he worked with Dominique Chesnoy-Marchais and Alain Marty. Towards the end of this period, Michael became interested in the workings of the cochlea and in particular the hair cells. He then (1985-1990) worked in three different laboratories – those of Jonathan Ashmore (Bristol), Paul Fuchs (Denver), Andrew Crawford and Robert Fettiplace (Cambridge) on various projects concerning hair cell function. Michael then worked for two years as a temporary lecturer in physiology at Bristol. During this time he managed to obtain independent funding (from the Wellcome Trust) for a project investigating the cellular mechanism of efferent inhibition of cochlear outer hair cells. In 1996 he moved to Keele. His main interests concern hair cell physiology and efferent control of hair cell function.

James Jones graduated in medicine (University College Dublin) in 1987. After a year as a house officer in Medicine and Surgery he returned to the medical subject that most fascinated him and enrolled in a BSc (Hons) course in physiology (1989). Ronan O'Regan's work on the central control of the carotid body stimulated James to

Above: Yoshihiro Kubo
Below: Eduardo Rios

refine his study of the regulation of the cardiovascular system by the 'black box', the medulla oblongata. O'Regan suggested that he work with the expert cardiovascular neuroscientist David Jordan, in the Department of Physiology, Royal Free Hospital School of Medicine (RFHSM) London. James was awarded a PhD in 1993 for his work on the central control of the pulmonary chemoreflex by University College London. At the Royal Free Hospital he was greatly influenced by the teachings of Michael de Burgh Daly and Andrew Ramage and, through interaction with these two scientists, diversified his approach to experimental physiology and pharmacology. From 1993-1995 he held a Wellcome Trust lectureship in the Department of Physiology, RFHSM and then returned to his *alma mater* in the Department of Human Anatomy and Physiology, University College Dublin. Generous support by the Wellcome Trust (UK) permitted James to run a relatively well-equipped laboratory in Ireland and he has continued to study vagal control of the rat heart. A recent antipode of previous science funding policy by the Irish government has altered the working environment dramatically.

He is currently a principal investigator in the new Conway Institute of Biomolecular and Biomedical Science of University College Dublin. The Institute is named after E J Conway whose seminal papers in *The Journal of Physiology* laid the foundations for the ionic basis of cellular resting membrane potential. James was promoted to senior lecturer in 2003, and his urrent research interests have expanded to include vagal paraganglionic chemoreceptors, accessory rat coronary circulation, frog carotid labyrinths, pulmonary venous system of muridae, central regulation of crural diaphragm, lower oesophageal sphincter and external anal sphincter.

Haruo Kasai is currently a professor in the Department of Cell Physiology at the National Institute for Physiological Sciences in Okazaki, Japan. He received his MD in 1981 and a PhD in 1985 from the University of Tokyo, and has since worked as a research scientist in the University of Tokyo, as a Humboldt Fellow at the Max-Planck-Institute for Biological Chemistry, and as an assistant and associate professor at the University of Tokyo.

Yoshihiro Kubo is currently professor in the Department of Molecular Physiology at the National Institute for Physiological Sciences. He was awarded an MD in 1985 and a PhD in 1989 from the University of Tokyo, and has since worked as a research scientist (Department of Neurophysiology, Tokyo Metropolitan Institute for Neuroscience), post doc (Howard Hughes Medical Institute, University of California) and professor of physiology and cell biology (Tokyo Medical and Dental University Graduate School of Medicine).

Eduardo Ríos was trained at the Universidad de la República in Montevideo, where he studied medicine and engineering, and obtained a degree in physics. After a few years as Instructor in Montevideo, he was demoted to Postdoctoral Fellow, and enjoyed working with Martin Schneider at the University of Rochester, New York. He has been at Rush University in Chicago since 1983. There he and friends Tom Shannon and Jingsong Zhou recently founded the Section of Cellular Signalling, largely dedicated to studying signalling by calcium in various types of muscle cells. Eduardo is indebted to the US taxpayer, who still supports the lab in spite of wars

and tax cuts. Among other things, this support allowed the Section to procure advanced microscopes with which the group is imaging calcium inside cellular stores. He is also grateful to the Universidad de la República, for giving him a permanent, albeit un-funded position, which allows him to keep in touch with the active scientific scene in Montevideo, and travel often to his hometown, Tacuarembó.

Experimental Physiology

The most recent meeting of the Editorial Board of *Experimental Physiology (EP)* was held in July at Merton College, Oxford. The editors, together with representatives of the Society and Blackwell Publishing, conducted the meeting in the splendid surroundings of this 13th century Oxford College which was once the home of William Harvey as Warden. The Chair welcomed our overseas editor Mohan Raizadi from the University of Florida, and also David Eisner and our two consulting editors, Abe Guz and Denis Noble, to their first meeting.

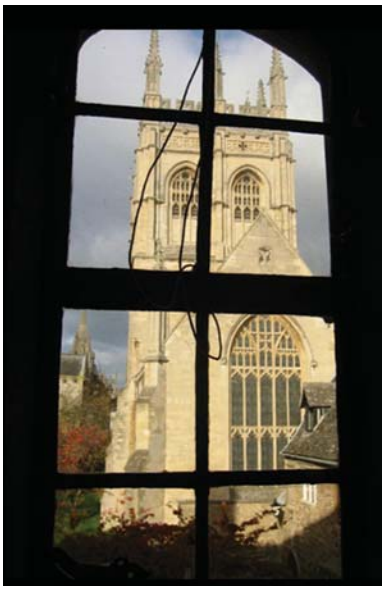
The perennial problem of scientific impact factors was discussed at length. The Board was clearly disappointed to see its impact fall for 2003; however, this was a trend seen in most physiology journals and was a concern that no doubt all editorial boards around the world are currently focusing on. Nevertheless, one year's result must be taken in context with the overall direction of travel of *EP* which has been progressive and adventurous. The Board was keen to gather data on articles that contributed to its impact and whether, strategically, publishing short articles from symposia was counterproductive. Although our North American editors are not as concerned about impact factor as their British colleagues, the issue of the Research Assessment Exercise regrettably looms over British academia where impact factors will probably become an important metric.

One area that *EP* is focusing on is computational biology with modelling integrated with experimental data to help explain physiological processes. Denis Noble and Peter Hunter are exploring the possibilities of developing databases with molecular and cellular information as well as models that could be stored for potential development into whole systems applications. A small committee is being put together to undertake a feasibility study to see whether a website can be coupled to the journal to hold supplementary information in a downloadable format that would host models associated with experimental papers.

Experimental Physiology's Editorial Board meeting in Oxford in July.

Left to right: Lucilla Poston, Christoph Korbmacher, David Paterson, David Eisner, Denis Noble, John Coote (Chair), Julian Paton, Mary Forsling, Godfrey Smith, Mohan Raizada, Abe Guz, Rod Dimaline and Jeremy Ward (Society Treasurer)

EP had a very successful re-launch at Experimental Biology in Washington DC last April. The Board felt that increasing *EP's* profile in the US was a major mission in the next 12 months.



Merton College, Oxford - venue for the EP Editorial Board dinner

Together with the publisher, it was proposed to increase the visibility of the journal at the Blackwell trade stand in San Diego for the IUPS meeting in April 2005. The Board is also exploring options to sponsor a symposium and host a reception where delegates will have the opportunity to meet editors of the journal.

The relationship between *EP* and *The Journal of Physiology* (JPHY) normally receives some degree of discussion at each Board Meeting. Although both journals have slightly different remits it was felt that there should be synergy between the two journals and that the Publications Committee should be giving both Boards clear directions as to the Society's expectation of their journals. The Society officers present proposed an historic meeting of senior editors from both journals in London at the end of the summer vacation. This first meeting was very successful, with friendly and frank discussions about the direction *EP* and *JPHY*. In the end it was agreed that both journals need to have an active dialogue.

Abe Guz posed the interesting question of how far we want to go in translation and integration. He pointed out that we do not publish clinical articles on man or pathology and wondered whether we should be capturing both physiological and pathophysiological studies as a part of our translation and integration remit. It was noted that there was a perceived divide between clinicians and physiologists, with some of the best physiologists working as practising physicians. The Board had agreed to

take this as a major item at its next meeting for further discussion.

Several editors had been working very hard to gather commissioned articles. These formed part of our Hot Topics series and were getting considerable attention in the literature. In particular, the recent Terry Thresher article with commentaries on the role of baroreflexes in hypertension that was commissioned by Julian Paton has received significant visibility. The Board was also delighted to hear that John Coote had accepted the invitation to deliver the Paton Lecture in Bristol next year at the first major annual meeting of the Physiological Society. We were also pleased to hear that John would be publishing his lecture in *Experimental Physiology*. In addition, several other prize lecturers from the American Physiological Society have also agreed to have their lectures published in *EP*.

The Board thanked Jill Berriman for her efforts as Managing Editor of *EP* and wished her well on her move to New York.

Prior to the Board's dinner, members had the opportunity to visit some of the historic sites at Merton College. In particular, the oldest ancient library in Britain, where they were shown the alleged spot where William Harvey (Warden of Merton College, Oxford – pictured above in 1654) used to work whilst 'on-call' in case the King (Charles I) required his services at Christ Church College (just up the road) after a difficult day's encounter with that Cambridge MP, Mr Cromwell.

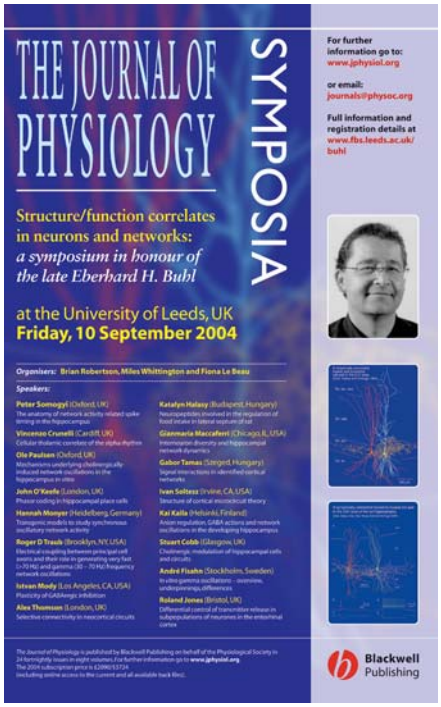
David Paterson
Deputy Chair, Experimental Physiology

The Journal of Physiology Eberhard Buhl memorial symposium

A *Journal of Physiology* symposium in honour of the late Eberhard H Buhl was held at the University of Leeds on 10 September, 2004

The University of Leeds was privileged to host a symposium in honour of the outstanding contribution to neuroscience from the life and work of the late Eberhard Buhl. Professor Buhl had been chair of Neurobiology and Head of the School of Biomedical Sciences in Leeds until is untimely death in January 2003. The meeting entitled *Structure/function correlates in neurons and networks* was held in the School of Biomedical Sciences, on 10 September, 2004. Scientists from the UK, many countries in Europe and institutes in the United States, each a leader in their field, convened for an intense day of talks and discussion in front of an audience of over 150 researchers. A broad spectrum of theoretical and practical disciplines was addressed, revolving around Eberhard's key research areas of cellular neuroanatomy, network function and brain rhythms. This diversity reflected the breadth of his contribution to science including: seminal work on the structural and immunocytochemical identification of interneuron subtypes; the profile and pattern of modulation of inhibitory synaptic activity; the topology of heterogeneous neuronal networks; functional characteristics of activated neuronal systems (both at the behavioural and reductionist level); the mechanisms of generation of neuronal rhythms associated with cognitive function.

The degree of importance Eberhard's work was, and still is, to the field of neuroscience was clearly illustrated by



the wealth of novel discoveries presented. Each topic had, as part of its fundamental origin, the 'flavour' of Eberhard's explicit and rigorous approach to his science. Whether this was in the form of valuable discussion or a more concrete extension of his published work each speaker recognised and credited his influence.

To lose such an influential friend, colleague, and contributor to the field at such an early point in his career caused hardship to many. However, the symposium was a positive affair once it became obvious that Eberhard's memory and influence was still very much in evidence, and will continue to be for many, many years to come.

Miles Whittington
Fiona Le Beau
University of Leeds, Leeds, UK

Proceedings of the Physiological Society Focused Meeting held at the University of Bristol from 4-5 September on *Viral gene transfer in neuroscience: new tricks of the trade* are due to be published in the January issue of *Experimental Physiology*.

Prize Lectures at the KCL Meeting

Biller Prize (Donald Ward), Bayliss Starling (Gerhard Giebisch), Wellcome Prize (Alexander Gourine), Annual Review (Robin Irvine) and Peter Baker (Ramon Latorre)

Whither physiology?

Dear Editor,

I have read with interest the articles in the last two editions of *Physiology News* (**54**, 40; **55**, 40) by Olga Hudlicka and John Coote which chronicled the demise of the Department of Physiology in Birmingham. If it is of any cheer to the outside world, the death of integrative and systems physiology here may have been exaggerated. They are very much alive and well at the University of Birmingham, just down the hill from the Medical School, in the RAE rated 6* School of Sport and Exercise Sciences. Indeed, our 10 full Members (with a combined 106 years of membership of the Society) and our numerous Affiliates are eagerly anticipating Christmas 2005 when, together with our 'Sport-Ex' colleagues, we are due to be re-housed in a new £16.5 million research building.

Written without the use of a Ouija-board…

Mike White
School of Sport and Exercise Sciences, University of Birmingham

Publishing *The Journal of Physiology*

After 125 years of being with the same publisher, *The Journal of Physiology* is now being published by Blackwell Publishing. 125 years is a very long time for any contract to be continually renewed and one wonders not only why the contract persisted for so long, but also why did the relationship with Cambridge University Press (CUP) finally falter? Many Members of the Society have been involved with *The Journal* over the years and therefore I am sure many will have views on both of these issues. For my part, as a past Treasurer of the Society, I naturally asked many individuals why the change to Blackwell. The standard answer I received was for financial reasons. This I found puzzling as from my own knowledge of the Society's finances, from dealings with CUP and with other publishers I was under the impression that CUP was still good value. This prompted me to fish out the figures. While I was Treasurer of the Society, I produced a report every year for the Committee showing a comparison of income/expenditure for various heads going back as much as 7 years. This document was a good starting point. I have now updated it with figures from the Annual Report for the last few years. This also includes the new Annual Report which takes us up to the end of 2003 when CUP's contract ended.

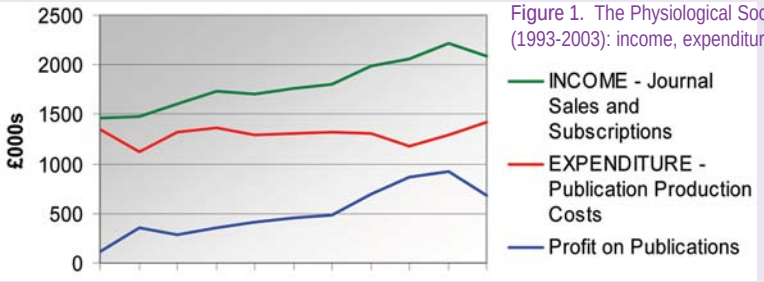


Figure 1. The Physiological Society journals (1993-2003): income, expenditure and profit

Figure 1 shows the data in relation to journal income, the costs of production and, therefore, the profitability. (It is not easy to identify the finances of *Experimental Physiology* separately from *The Journal of Physiology* over the period shown and therefore combined figures are shown). As can be seen there has been a systematic increase in journal income from £1.47m in 1993 to a peak of £2.22m* in 2002. This has always been surprising since there has been continual concern that slippage in subscription take-up would reduce journal income. The market has always been much more resilient than we anticipated.

The costs of production have remained fairly constant at about £1.3m. This is equally surprising given the fantastic cost benefits introduced with improved technology. On the other hand, technology has been expensive to install and there have been many initiatives to reduce publication time and to improve the impact factor. (Whether or not these have been successful is another issue.) For example, I remember a time when the costs of using a courier to send out manuscripts to reviewers was costing £70k per year! The overall result of improved income with constant production costs is that the profitability has increased systematically and substantially from £120k in 1993 to a peak of £925k in 2002. I consider this to be a phenomenal increase and is much more than that produced by comparable journals belonging to our sister learned societies - even those published by CUP!

This profitability certainly reflects an 'active' exchange between the Society and CUP. By this, I mean an active dialogue between the parties and regular reviews of working practices, including regular reviews of the contract. The previous major review of the contract was in 1998/9. This began in relation to the contract of *Experimental Physiology* in 1998 when an extensive tendering process took place. A key financial issue in assessing any prospective publisher was the issue of the cost of printing which cannot be ascertained with any certainty (because it depends *inter alia* on world paper costs). It was extremely important to establish the basis on which projected printing costs were calculated, as otherwise any 'fly by night' publisher could produce a set of accounts showing projected profits so much better than any other tender. Being clear about printing costs is crucial since the cost of printing is by far the largest single item of expenditure of the journals. CUP agreed to meet the best deal we were offered and subsequently offered the same terms when the contract for *The Journal* came up in 1999. In addition, there were clearly several other factors that supported the view of staying with the incumbents. As well as the obvious ones, there was the subsidy received by CUP on office space within the CUP site (and the accompanying benefits to staff – leisure facilities, subsidised canteen, etc.), the

*For consistency the figures quoted are taken from the annual Report for any given year. Occasionally a subsequent Annual Report will give different figures

ongoing and developing initiatives for promotion of the journals and, not least, the fact that the subscription list was the property of CUP! I do not know how this latter detail arose, but it could lead to financial uncertainty if CUP ever felt that they were unfairly jilted at the time of a change of publisher. (It is interesting to read in the Annual Report that journal subscriptions have recently slipped and presumably this led to the drop in income in 2003 shown in Fig. 1). In the light of all these considerations, the decision to stay with CUP in 1998/9 was unanimous.

Since that time, there have presumably been changes in circumstances of which I'm unaware, but given the data in Fig. 1, I was surprised that the decision was made to change publishers on financial grounds. Has the new publisher produced evidence that one of their comparable journals has turned in a similar profit in recent times? Whether or not it has, the data is Fig. 1 will provide a benchmark with which to monitor their performance. And, of course, this profitability does not include the 'windfall' gains that the Society has just cashed in. Thus, there is a now much reduced editorial function in the Publications Office and the typesetting work is now out-sourced to India. Whatever results Blackwell produce, 125 years will be a hard act to follow.

Philip J Harrison
Department of Physiology, University College London, London, UK

Dafydd Walters replies:
Phil Harrison is correct in saying that 125 years is a long time for the Society to have had a contract with Cambridge University Press (CUP) to publish *The Journal* but I must correct the misapprehension that the decision on the new publisher, Blackwell, was taken solely or even mainly on financial grounds. It is important for him and other Members to realise that this was not the case. I did outline the tendering procedure and the factors considered in the decision in my report (Annual Report of the Physiological Society, 2002, p. 3). It seems that they need re-iterating here.

The contract with CUP has come up for renewal periodically since 1878 but, as the last occasion drew near, Council thought it best to ask for a thorough reappraisal involving a rigorous tendering process where bids were to be invited from all relevant scientific publishers. This change in practice from a semi-automatic renewal of the contract was taken because there were concerns about the rapid increase in electronic publishing expected in the near future and because an open and transparent procedure would be needed to ensure that the best possible publisher was selected for the Society's journals. A Tendering Group was established, which I chaired and which comprised three people from the Executive Committee and four representing the Editorial Boards of the journals. The Group met three times to define what we felt were the important factors in our decision making and to decide on our tendering document, to shortlist publishers from the seven that ultimately submitted bids and, finally, to interview the four short-listed publishers. It was an early decision of the Group that the quality of the journals' content and presentation was not to be compromised at any price.

The factors probed in the interviews included each publisher's procedures for ensuring quality (covering editing and production), plans for the future (including marketing strategies and how the electronic revolution would be handled), how any change of publisher would be dealt with, working relationships with the Editorial Boards and, finally, risk management and financial considerations. The decision process was so structured that financial aspects were discussed last and by the time we reached this stage it was apparent that there was unanimous agreement on the choice of Blackwell Publishing. The fact that their financial package was advantageous to the Society and the journals was a welcome bonus.

I hope this description of the sequence of events goes some way to reassuring Phil Harrison and those of you who felt that the Society may be being run by totally mercenary individuals. Nothing could be further from the truth. However, the Trustees of the Society do have to ensure that the Society is financially sound, now and in the future, to enable it to carry out its objectives. I hope that everyone will be satisfied when the accounts for 2004 are available and the effect of our transfer to Blackwell Publishing will be seen against the background of no alteration in the high standards of publication of the journals. In addition, the Tendering Group believes that we have a partner who will face the future with imagination and flexibility.

One hundred and twenty five years is a long time and for a Luddite like me who still hankers after the thick hard cover volumes of T*he Journal of Physiology* with the pink dust sheets and that lovely linen-rich cream paper, it was not easy to get to this point. But the future beckons and the Society and its journals need to be there in the vanguard.

Dafydd Walters
Chairman of the Executive 2002-2004

Time to communicate?

Dear Editor,
I would like to offer a suggestion that might help those who felt that they could engage with the public about their scientific interests by writing. I believe that the Royal Society once helped such authors through an organisation called COPUS; could this be revived by some scientific organisation with helpful referees? The reason for my asking comes from a personal experience that I would like others to avoid!

Briefly, I was lucky enough to be a young physiologist who came early under the influence of Joseph Barcroft. This led to a very exciting career and, finally, to a small unit of my own in a department of obstetrics and gynaecology at a London Hospital where we tried to think about fetal growth. After retirement, I thought to contribute by trying to write a book for an intelligent public on how the fetus was fed to grow before birth. I did not want to be pressurized so I did not try

for a publisher until it was completed. No publisher would even look at the manuscript, most did not even reply and one excelled by telling me that I did not have a profile — in spite of giving them a cv (I finally self-published on a modest scale).

As an ordinary mortal I certainly would not have had the time to write such a book whilst working — neither would I have had the perspective. I agree with you that some of biology is too invisible and think that biology in schools might well start with human anatomy and physiology and all its everyday applications, and work back to the cell and genes etc. At least the dogfish gave us some anatomy and we saw tadpoles developing!

Maureen Young
Cambridge (former Professor of Perinatal Physiology, St. Thomas's Hospital Medical School)

Editor's note:
Do any other readers have similar experiences (good or bad?) of writing about science for a wider audience and trying to get into print? If so, please write in and tell us about them.

COPUS has shut down its grant schemes, but both the Wellcome Trust and the DTI (via the Sciencewise scheme, www.sciencewise.org) fund projects in public communication and public engagement. However, their schemes do not address the specific questions of how to write or how to publish popular science. Some information and articles about the former can be found at the site for the *Telegraph's* Young Science Writer (www.science-writer.co.uk) or the site of the Association for British Science Writers (www.absw.org.uk). Perhaps if enough Society members have useful tips *Physiology News* could publish a guide for the interested.

Young Physiologists' Symposium, KCL

Charlotte Waters looks ahead to the biggest YPS ever, planned to take place at the King's College London Meeting in December

When I agreed to be the local organizer of the young physiologists' symposium at KCL, I had understood it to be a relatively small affair with about 20 affiliates giving presentations on their current research. Little did I know then that it was going to turn into the largest YPS meeting ever attempted by the Society (topping 70 presenters), or that the backgrounds of the attendees would be as varied as their subjects.

The reason for the large attendance is the presence of 42 members of the Sociedad Chilena de Ciencias Fisológicas – the main Society Meeting is being held jointly between the UK and Chilean Physiological Societies, with students attending both meetings.

The last time this happened was in November 1999; 25 students gathered for a YPS in the Gran Hotel Pucón, Pucón in Chile. Every attendee gave an oral presentation, all in one day, with eight of those being from the UK and Ireland. This time round we not only have affiliates from Chile, but also from the UK, Spain, Denmark and the Ukraine. I am therefore exceptionally grateful that there is also an organizer based in Chile – Paola Casanello from the Universidad de Chile in Santiago.

The YPS at KCL is an open meeting, without a specific topic. We have received abstracts on leptin through to nitric oxide to potassium channels to nervous stimulation of man. As well as excellent presentations from all the attendees, there will also be two keynote seminars – one by Michael Duchen from UCL (an expert in mitochondrial biology), and the other by Juan Bacigalupo, from the Universidad de Chile (who specialises in neurophysiology). The meeting was also advertised as taking place in an informal and friendly atmosphere – the audience will be comprised only of the students taking part, and so the idea of giving an oral presentation has become less stressful, and I have had a number of students asking to give a talk (not a usual occurrence).

Paola Casanello, Co-organizer from the University of Chile, Santiago (top) and Charlotte Waters – Local organizer of the YPS at King's College London (above).

On a personal note, I must confess that I am rather looking forward to the meeting, despite the level of organisation required and all the work that will needed to make it a success. As the meeting is just before Christmas, Paola and I hope that we can make the YPS fun and worth the trip.

Charlotte Waters
Centre for Cardiovascular Biology and Medicine, King's College London, UK

International Society for Arterial Chemoreception (ISAC) XVIth Conference - Sendai, Japan, May 9-12, 2005

ISAC is an international forum for non-clinical and clinical researchers with specific interest in the mechanisms of cellular oxygen sensing and adaptation and the chemical control of breathing in general. The XVIth Meeting will cover all aspects of chemoreception including: control of gene expression by HIF system: erythropoietin production, vascular endothelial growth factor, glycolytic enzymes, tumor growth factor; oxygen sensitivity in CNS neurons; hypoxic pulmonary vasoconstriction; CO^2 and O^2 chemoreception: peripheral and central mechanisms. Website: http://www.isac-web.org/files/sendai1.htm

How the Society works

The machinations of the Society are a mystery to many. To some extent detailed committee structure is of no importance or interest to the majority of Members, but you do need to know who to go to if you have questions regarding a particular area, or wish to be more involved.

Council and the Executive Committee

The Society is governed by a **Council** of 27 Members who are formally elected by the membership at the AGM (although many Members post in their ballots).

Council meets 3-4 times a year to discuss policy and strategy. Council elects, normally from amongst its number, an **Executive Committee** consisting of a President, Chairman, Vice-Chairman, Treasurer, Meetings and International Secretaries. The Editorial Board of *The Journal of Physiology* also sends a representative to the Executive Committee. This Committee meets every 8 weeks or so and oversees the day-to-day running of the Society.

Sub-Committees

Much of the actual 'work' is undertaken by **sub-committees** and **working parties.** These either implement Council strategy, or put forward new ideas in their particular area to Council. The Chair of each of these is shown on the flowchart (see below), with the administrator responsible for servicing the group given in brackets.

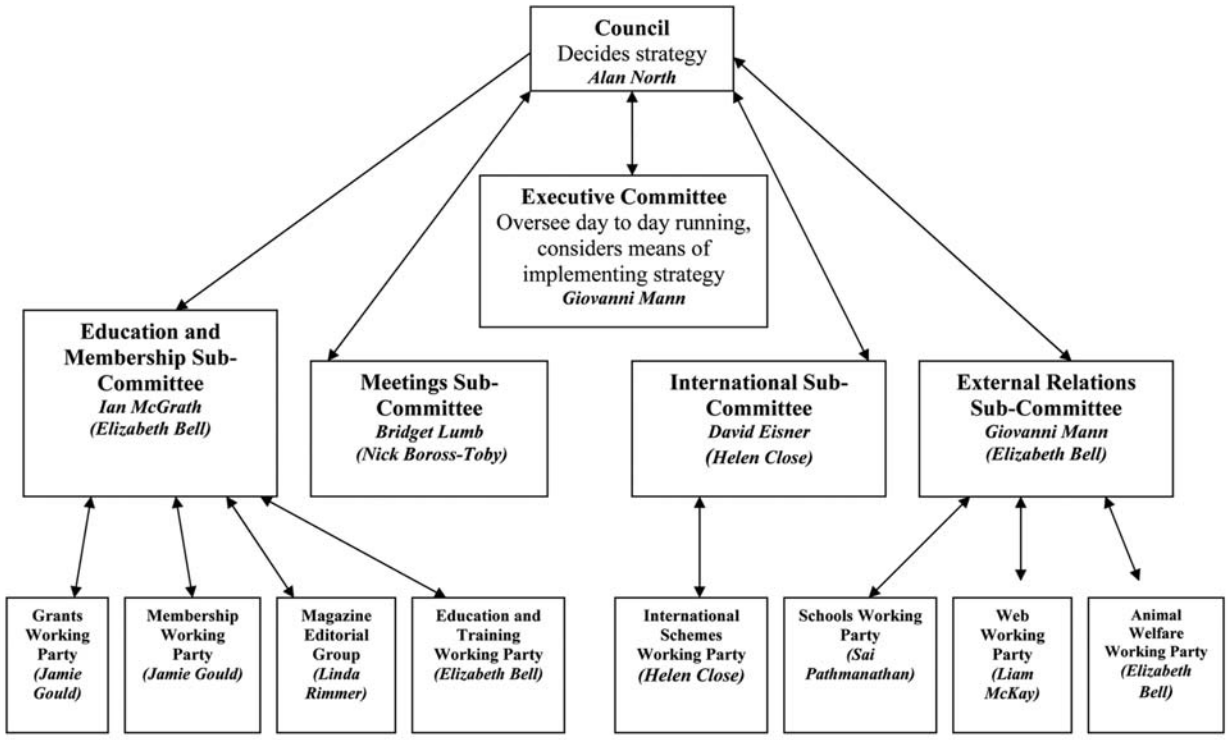
Many sub-committees and working parties have non-Council Members on them; if any Member is interested in a particular group contact the Chairperson, either directly or through the relevant administrator.

Affiliates are represented on several of the groups. There are two Affiliate observers to Council, and they or other Affiliates are involved in sub-committees and working parties. Again, more participation is always welcomed.

There are a couple of other committees Members might be interested in. The **Audit Committee** oversees effective working of the Society. It includes non-Society Members and is chaired by a non-Executive Committee member, Michael Rennie. The **Honorary Members' Nominations Committee** comprises some Council and non-Council members, and makes suggestions for nominations of Honorary Members to Council. This is chaired by the President, Alan North. Any suggestions from Ordinary Members regarding nominations should go either directly to him or through David Sewell at the office (dsewell@physoc.org). Council also has another Nominations Committee which deals with nominations to Executive Committee positions.

Maggie Leggett

Decision making structure



Notes:
Sub-committees implement strategy in their area. This is in response to overall strategy from Council. They also work up suggestions to put to Council. They can comprise a mixture of Council and non-Council members.
Working parties concentrate on particular areas, and respond and report to the relevant sub-committee. They too can comprise a mixture of Council and non-Council members.

Affiliate grant

In October, I was awarded an Affiliate grant which helped support a 2 month period of research collaboration between myself and Romain Meeusen of the Department of Human Physiology and Sports Medicine, Vrije Universiteit Brussel, Belgium. During this time we completed a project to examine the role of brain neurotransmission in the development

The research group from Vrije Universiteit Brussel educate Phil Watson in the delights of Belgian beer

of fatigue during prolonged exercise. The work, completed in Brussels during an 8 week period leading up to Christmas, has significantly contributed to the completion of my PhD thesis and should lead to a publication. It has helped foster a relationship for future collaboration between our research groups. I am extremely grateful to the Society for their support.

I feel this period of collaboration has been a beneficial and rewarding experience. Professor Meeusen and his research group made me feel very welcome throughout my stay in Brussels, including attempting to teach me some basic Flemish and educating me in the delights of Belgian beer.

Phil Watson
School of Sport and Exercise Sciences, Loughborough University

Channels to networks

The School of Biomedical Sciences, University of Leeds hosts a one day Young Physiologists' symposia on 23 August, 2004

The general idea behind the Young Physiologists' Symposia (YPS), sponsored by the Physiological Society, is that affiliate members are given the opportunity to co-ordinate small, themed meetings in which postgraduate students and junior post doctoral researchers can present their work in a friendly and informal atmosphere, i.e. we can shine on our own (somewhat smaller) stage and leave the bright lights of Broadway to the stars!

These events can be held in conjunction with Society Meetings or as stand-alone events. The previous YPS at the University of Leeds was held alongside the Leeds Physiological Society Meeting in September 2002. This time, however, we organised a smaller stand-alone event because … well, why not? What else are you going to do on a wet Monday in August? This is the North you know.

So, we found an affiliate to do the co-ordinating (that will be me then!), decided on a theme of *Channels to Networks* and along with Hilary Murray and Darragh Freir, my fellow chairs, gathered together 24 presenters for the day. The presentations were a mix of oral and poster communications with participants from the universities of Huddersfield, Strathclyde, Oxford, Liverpool John Moores, UCL and the University of London, School of Pharmacy as well as from Leeds itself.

The day was organised into three speaker sessions and a one hour poster viewing session following lunch. The participants at the Leeds YPS had a variety of presentation experience, with some first-time speakers also taking part. All the presentations given were of an exceptionally high standard and demonstrated an impressive calibre of research. On the whole everybody seemed to have an enjoyable and worthwhile day with participants at the very least taking away with them a sense of achievement at having survived their first presentation - some people may have even learnt something!

The prize for best oral communication was awarded to Rhiannon Meredith., currently a post-doctoral researcher with the Neuronal Oscillations Group (NOG) in the Department of Physiology, University of Oxford. Her presentation *Developmental profile of spike timing dependent plasticity in layer IV to layer II/III synapses of*

Transfer news/promotions

Sue Wray has been appointed Head of the Department of Physiology at the University of Liverpool.

Congratulations to …

Ole Petersen (University of Liverpool) who has been elected an Honorary member of the Hungarian Academy of Science.

Nancy Rothwell and Roger Lemon who have been elected to the Research Defence Society Council as Chairman and Honorary Secretary respectively.

Society staff

The Society welcomed Nick Boross-Toby to the London Office in October as Meetings Administrator and Elizabeth Bell will take over as Deputy Executive Secretary and Head of External Affairs in January.

Two new staff have joined the Publications Office in Cambridge. Liam McKay has been appointed as IT Manager to replace David Gunn, and Sue Ecob has been appointed as a part-time Distribution Assistant.

Carol Huxley, previously Senior Production Editor, will replace Jill Berriman as Managing Editor. Jonathan Goodchild replaces Carol Huxley as Senior Copy Editor and Jill Berriman has rejoined the Society to work remotely from New York as a copy editor.

From the top:
Carol Huxley, Liam McKay and Jonathan Goodchild

Leeds University poster presenter Joanne Driver and I discuss her work at the poster session

mouse barrel cortex detailed some really interesting research into spike timing dependent LTP in developing mice and how this persists in the adult.

Ruth Taylor, a first year PhD student from the Department of Physiology, UCL won the prize for best poster presentation on the *Effect of the neuropeptide PACAP on the slow calcium-activated current, sI_{AHP}, in hippocampal neurons.* Ruth's data was extremely impressive, even more so considering her PhD project is still in its infancy.

The day's events were, naturally, brought to a close with a few drinks at the 'local' and over dinner the presenters had a chance to speak to each other in more detail'

Thanks are due to all the presenters who attended and we hope to have given those who took part an insight into the work of related research groups and, with any luck, enthusiasm to present again! Particular thanks to everyone who helped me organise the event, including Sai Pathmanathan from the Physiological Society and Neil Morris from the University of Leeds, for his help with judging the presentations.

Helen Garner
School of Biomedical Sciences, University of Leeds

Rhiannon Meredith adds:
This was the first Young Physiologists' meeting I had attended and I got a lot out of the day, both in terms of the research talks given and from chatting with other PhD students and young postdocs about their latest experiments and life-in-the-lab. The speaker sessions were well organised and given the diversity of topics covered from cellular neuroscience to systems physiology, were grouped accordingly for the three sessions. From my perspective, presenting recent findings concerning the role of different NMDA receptor subunits in synaptic plasticity in the cortex at a small meeting such as this one proved a valuable exercise both in terms of presenting new data in a comprehensive style and hearing the questions that fellow neuroscientists raised from these findings. The latter will be particularly useful in the coming months as I sit to write-up the findings for a paper! All-in-all, a worthwhile and enjoyable day.

Communication skills workshop

Science in Schools

Looking through many of the job vacancy advertisements, it is evident that good communication skills are commonly deemed necessary for a variety of positions in biological sciences. The Physiological Society held a workshop on this topic in Guy's Campus, King's College London for Affiliate Members on 4 August. The aim of the meeting was to help Affiliates improve their communication and presentation skills. In addition, we learned about going into schools to speak about science to students and teachers alike.

The opening session was provided by Janet Wilkinson (UK Grad). This involved a discussion of the general aspects of communication, both verbal and non-verbal. Secondly, we had an excellent talk, group discussion and vigorous recruitment campaign from Ted Griffiths from Biomedical Research Education Trust (BRET). BRET is a charity whose main purpose is to provide secondary schools with information and speakers about the humane and responsible use of animals in medical research. We were provided with an insight into communicating an emotive and potentially divisive topic with secondary school students and their teachers. BRET provide training and information packs for speakers on their website (www.bret.org.uk).

The final section of the workshop was organised by Janet Wilkinson and helped us put into practice the skills discussed in the opening talks. The object was to convey our research to another participant, who passed it on to another who would then report to the whole group. This 'Chinese Whispers' exercise was surprisingly successful and it was enlightening to hear someone else give a brief description of your research.

Overall, I feel I left better prepared and willing to go to talk about science in schools with less trepidation. I believe the Society's Members and Affiliates have a valuable role in this area. Sharing our knowledge with the outside world, specifically with secondary school students, would enable us to both educate the public and recruit future scientists. Finally, on behalf of all the participants, I would like to thank the speakers for an informative and very enjoyable day, particularly workshop organiser, Sai Pathmanathan from the Physiological Society.

David Archer
School of Medical Sciences, University of Aberdeen

The BA Festival of Science 2004

The responsibility of being a scientist

This year, as part of the 2004 British Association for the Advancement of Science (BA) Festival of Science in Exeter, the Physiological Society held an engaging and informative session on the responsible use of animals. Four speakers gave presentations that covered a variety of issues including why animals are used in biomedical research, the patient's viewpoint, the

public's perception and where do we draw the line?

Zafar Bashir (Department of Anatomy, University of Bristol) chaired the event. He started by asking the audience: 'How many of you would be happy to see medical research on animals completely stopped immediately?' By way of a show of hands, around half of the audience indicated that they **would** like animal testing stopped now. I was quite surprised by this, as out of all the school talks I have given, this was the first time a majority of the audience were against animal use in research. Zafar then explained a bit about physiology and the Society before introducing the speakers.

Bridget Lumb (Department of Physiology, University of Bristol) was first to speak on the need to use animals. Bridget addressed the question - what can animals tell us? Attention was drawn to the similarities between man and mouse and, as a consequence, the diseases that we have been able to cure as a result of using animals in biomedical research.

Vicky Cowell (Seriously Ill for Medical Research - SIMR) spoke about the patient's perspective, as her daughter suffers from cystic fibrosis and diabetes. She also showed a video, *The Right to Hope* - a poignant story of Andrew Blake's life. Andrew Blake (founder of SIMR) was diagnosed with Friedrich's Ataxia and understood the need for research on animals to continue, yet at the same time his compassion for animals was also evident. The audience (mainly sixth formers) were completely silent following the video.

Clare Stanford (University College London) gave an interesting insight into quality of life issues. Clare provided some information on the various organisations conducting research and how much money these raise. Based on this, our priorities are cancers and heart disease. But what about mental illnesses? I found it alarming to hear that more young people die from suicide than road traffic accidents. Why is far less money raised for these conditions? Perhaps it is because many

Festival of Science speakers, clockwise from top left: Zafar Bashir, Russell Foster, Care Stanford, Vicky Cowell

people just assume those with mental illnesses should 'snap out of it' and those who are clinically obese should 'stop pigging out' … but what if these patients are genetically predisposed to becoming manic depressives and overweight? Surely this would be worth researching? Researching with animals?

Branwen Morgan's (Coalition for Medical Progress) talk was based on people's concerns about the use of animals in research (as gauged by a MORI poll) and the need to communicate with the public whilst ensuring vital research continues. Examples of CMP's activities were given. Branwen also described her personal experiences of animal research and how she was not comfortable carrying out such experiments herself.

Zafar ended the session (before questions were put to the panel) by revisiting the question he posed at the beginning. This time around those in favour of stopping animal experiments were less than 5% (about three hands!). So when animal research is explained in context people realise that there are real benefits for both humans and animals. Most of the students explained that they had never been told this side of the story, and did not realise that many of the procedures on animals were mild ones, e.g. taking blood samples. Many were also under the impression that we were going to talk about cosmetic testing!

Special thanks must also go to Ted Griffiths (Biomedical Research Education Trust) and Bridget Lumb who helped with the *BA-ckchat* programme over lunch. This involved groups of school students chatting to the speakers about the topics raised in the morning's session, what they thought about the topic and to get clarification on points that they were not sure about.

The afternoon session was *Fundamental Research: What's the Point?* organised by the Biosciences Federation (www.bsf.ac.uk). Maggie Leggett had arranged all the speakers before leaving the Society and was present in the audience that afternoon to see the fruits of her hard work! It was another excellent session with scientists discussing their research findings and, although there was no direct benefit to the public (i.e. no diseases were being cured), they showed that fundamental research has led to some of the greatest and most unexpected discoveries in the world. Sue Assinder (University of Wales, Bangor) chaired the event.

Dafydd Walters (St George's Hospital Medical School) spoke about the miracle of birth - how the transition from breathing fluid to breathing air takes place in a newborn baby's lungs. We all learnt some interesting facts on surfactant, with a demonstration (projected onto a screen via an OHP) of surface tension using water, chalk dust and some detergent in a syringe (you had to be there!).

Susan Jobling (Brunel University) discussed the topic of environmental hormones and the feminising of male fish as well as other species. Susan also enacted the communication between the pituitary gland and the ovary – using mobile phones. She was the pituitary gland, and I was called upon to play the ovary (not many people can say they've been an ovary before!) Susan then sent me a text message saying, 'Make oestrogen' - much to the amusement of the audience.

Jon Copley (Southampton Oceanography Centre) enlightened us on the myriads of species living

without sunlight and oxygen in deep-sea vents. It was intriguing to hear about the discovery of hydrothermal vents and how marine creatures have adapted, even to the point of evolving a new form of haemoglobin.

Russell Foster (Imperial College) chose *Rhythms of Life* for his talk, and spoke about biological clocks and how this modulates our physiology and behaviour. It was fascinating to find out how research has progressed and how different species have different diurnal cycles leading to the various complex behaviours.

Both the Society and Biosciences Federation sessions covered aspects of the Biology GCSE and A-level syllabus and were part of the BA Young People's (14-19) Programme.

The Festival received a huge amount of press coverage over the week with stories also appearing in the *London Metro!* During the presentation by the Association for British Science Writers many well known science correspondents (including Vivienne Parry, Pallab Ghosh, Tim Radford and David Derbyshire) dropped in to tell us how they fell into science journalism and what the pros and cons are of working on television, radio and for national newspapers.

Several Society Members took part in other sessions at the Festival too. Geraldine Clough (University of Southampton), Dave Bates (University of Bristol) and Angela Shore (Peninsula Medical School, Exeter) took part in *Small is Beautiful* organised by the British Microcirculation Society. The session included several hands on demos and two of the other speakers (Faisel Khan, University of Dundee and Peter Mortimer, St George's Hospital Medical School) got national press coverage.

Graham Collingridge (President, BA Medical Sciences Section) spoke about synaptic plasticity in *Memories are made of this* and was mentioned in the *Telegraph*, *Independent* and even appeared in a photo in the *Times* the next day (with a model of the children's television character, Morph).

As well as the usual programme of scientific events on campus, there were a variety of programmes off campus, also known as *BA in the city*, which included trips to Bickham Farm, Sidmouth Observatory and the Eden Project.

Each evening broadcaster, Quentin Cooper reviewed the day's events in X-change, with a panel of festival speakers. This also gave members of the public a chance to question the panel in an informal setting – i.e. over a drink at the Balcony Bar. This was also a useful networking opportunity for the science communicators amongst us!

Overall a fantastic festival this year, with plenty of scientific celebrities to hobnob with. The weather was great too… which always helps!

For further details about the BA, please see www.the-ba.net. Contact Sai Pathmanathan if you are interested in attending the Festival next year or getting more involved in science communication events (spathmanathan@physoc.org or 020 7269 5727).

Sai Pathmanathan

BIOSCIENCES FEDERATION

Physiologists may be interested in four important initiatives that are currently occupying the Biosciences Federation.

Securing more realistic funding for HE science teaching

Last year, the Federation and others argued successfully to the Funding Councils that the biosciences should not be placed in a separate, lower-cost, funding band from the physical sciences. However, the battle to secure a more realistic unit of resource for the whole of science teaching has yet to be won. Federation President Tom Blundell held discussions with his counterpart at the Royal Society of Chemistry in September with the aim of establishing a strong joint case to be made to the government. This has the benefit that the government cannot accuse either discipline of pleading a self-interested special case.

Report of the impact of science funding policies on the health of the life sciences

The government believes that in order to compete in the global market place Britain needs fast-moving and innovative companies. These, in turn, need to be supported by an excellent science base, with the mechanisms in place to develop research discoveries into new products and services. It is on this basis that the government has invested so heavily in underpinning science infrastructure in successive comprehensive spending reviews. It has been investment with a purpose, and accompanied by increased micro-management, a drive to bring researchers closer to the users of their research outputs, and for greater accountability by the recipients of funding.

The Federation is working on a report that assesses the overall outcome from the considerable investment, particularly in relation to the capability and capacity of biosciences research. It will seek to make recommendations on how government policy on science and innovation could be modified to be even more successful in creating health and wealth for the nation from the biosciences sector. In order to inform this report, the Federation distributed questionnaires at the end of September to academic Heads of Department, and to research managers in bio-industry, that sought views on matters such as how infrastructure funding has benefited research, how problematic is the increased micro-management, the likely impact of full economic costing, and how to encourage greater industrial investment in R&D.

Science policy priorities for the next government

In 2001, the Institute of Biology and its affiliates, including the UK Life Sciences Committee, canvassed views on what should be science policy priorities for the government elected into power in that year, and published the consensus opinion in a very

successful Parliamentary launch. The Science Minister, Lord Sainsbury, commented that the findings were very much in line with government thinking and that the report had been valuable.

Now that the Institute is a member of the Biosciences Federation it has invited the latter to conduct a similar survey in advance of the 2005 election. Member societies have been asked to return their top six science policy priorities to the Federation by the end of 2004.

Enthusing young people with the excitement of the life sciences

Much has been made in the media about young people abandoning the physical sciences, but an examination of Higher Education Statistics Agency data shows that the number of university students has been declining in recent years in some sectors of biological sciences as well. On the recommendation of member societies, the Federation organised a working dinner earlier this year, at which invited guests discussed how to maintain the current excellence of the life sciences. The meeting identified the drift away from science in secondary education as an important contributor to the decreasing flow-through of talented young people into science careers.

The Federation is very pleased that Michael Reiss from the Institute of Education accepted our invitation to chair a subsequent working group on enthusing young people with the excitement of the life sciences. Such is the growing reputation of the Federation that the working group attracted a high quality membership from education and industry. It is tasked with producing an influential report by summer 2005 on how to reverse the trend for pupils to lose interest in science as they progress through secondary education.

Mike Withnall
Biosciences Federation

New Fellows

Graham Dockray (*above left*), Professor of Physiology at the University of Liverpool, and Nancy Rothwell, MRC Research Professor of Physiology at the University of Manchester, were elected as Fellows of the Royal Society in 2004. Both are well-known to many in the Physiological Society and, of course, in the UK bioscience community more generally.

Graham Dockray did his BSc and PhD in zoology at Nottingham and a postdoc at UCLA before becoming a lecturer in physiology in Liverpool in 19??. His research looks at the ways cells in the upper GI tract use hormones such as gastrin and cholecystokinin to communicate with one another and to control cell growth, epithelial organisation and function, and food intake.

Nancy Rothwell (*above right*) did her BSc and PhD in London at Queen Elizabeth College, and was a postdoc and a Royal Society Fellow at QEC before her move to Manchester in 1987. Her early work was on brown adipose tissue, but she soon moved on to studying the central control of thermogenesis and fever. This led her to an interest in cytokines and their role in fever, stroke, and many other conditions.

Neither thinks their fellow scientists have started to treat them any differently since the news came out. 'Scientists judge you on your work', says Rothwell. But both agree that there are more people than before seeking their opinion or wanting them to do things, both inside and outside their universities. Interestingly, both have recently taken on major new roles in their universities as Vice President for Research (Rothwell) and Pro Vice Chancellor for Research (Dockray). So what does a 'university research Czar' actually do? Dockray says he has 'been meeting the heads of all 43 units of assessment that Liverpool submitted in the last RAE'. Rothwell only officially started her new job when the merged Manchester University went live at the start of October, and sees one of her key roles as 'taking an overview [across the University]…helping identify the best ways to do things and spreading that knowledge through the University'.

Both Rothwell and Dockray feel that the Royal Society's ability, as an independent national scientific academy, to comment authoritatively on scientific issues make it a body with a unique position in the UK. But both agree that UK bioscientists still need to do more to influence politicians, opinion formers and the public. Should the Royal Society be the vehicle for any of this? Dockray says that 'The Royal Society [is] not a lobbying organisation per se… we need a range of bodies, from the Royal Society, to "ginger groups" like Save British Science, to the learned Societies, to all play a part'. Rothwell highlights the need for UK bioscientists to speak with a unified voice, through organisations like the Bioscience Federation, to maximize their influence.

Where do the new physiology FRSes stand on that burning issue for UK physiologists, discipline identity and departmental structures? Physiology Departments or Schools of Biomedical Sciences? 'The key is that the structures [whatever they are] don't get in the way of scientific collaboration', says Rothwell. Dockray points out that the larger 'School' structures that have gradually taken over in many universities make it easier to put serious investment into new scientific areas and technologies. He agrees that getting the organisational structures right is vital: 'You have to build in [to your structures] a sort of "mechanism for perpetual renewal"... but you also have to create the stable background - in terms of things like space and close colleagues – that researchers need'. Both new Fellows feel that physiologists are poised to take advantage of the possibilities opened up by the genome projects, and notably both have used whole animal models and transgenics in their work. 'There is clearly a demand [in industry and elsewhere] for people with traditional physiology skills,' says Rothwell.

One final thing we would really like to know; how do they find the time for all the stuff they do? 'Lists and planning' says Rothwell, '…and the usual female skill of multi-tasking!' Dockray agrees about the need for time management. 'You titrate the energy you have against [all] the ways to expend it… prioritising where you can and saying "no" when you reach capacity'. And having the right helpers and co-workers is also key. 'Having great people around to support me', says Rothwell.

Austin Elliott

The multi-coloured golf umbrella

For this special festive season column, I thought I would tell you a little story.

Once upon a time, somewhere in the UK, there was a medical school. This medical school was fairly typical. The building was showing its age. The drains and sinks stank, especially after the ventilation was turned off at 5 pm. The smell of phenol-chloroform mixture would often waft down from the molecular biology labs upstairs. The cleaners came every few weeks to re-arrange the dust on the floor, but avoided the really nasty bits under the benches, and most of the labs (too hazardous). The tops of the 1970s wooden benches were thick in accumulated grime, because there were no technicians left to clean them (cut-backs and voluntary redundancies). And it was always dark. The windowless corridors were gloomy, since even the light fittings that worked only had half the number of fluorescent tubes they were made for (the rest had been removed in an early 80s 'electricity economy drive'). So half the proper number of flickering bare fluorescent tubes shed a sickly light as the workers scurried along.

Then, one day, strange things started to happen.

First, extra cleaners started to appear. Or, at least, the same cleaners appeared more often. Rubbish was cleared every day. Corridor floors were scrubbed and polished every week - even the dark corners that were usually ignored. Posters and notices stuck on the doors and walls were pulled down, and the lab staff sternly admonished not to put them up again. The next week painters came and repainted several corridors in sunny yellow-white tones, rather than the usual institutional pale green.

The staff was surprised, and asked each other what it could all mean.

Next, something truly astonishing happened. A man in brown overalls appeared, and began to put fluorescent tubes back in the light fittings. Not all of them, to be sure, but all the light fittings in the main corridors. And then he started fitting diffuser panels to the light fittings.

The staff was amazed. The light fittings had had no diffuser panels since half the tubes had been taken out all those years ago. Where had these diffuser panels come from? Had they been hidden away somewhere for nearly two decades? Had they been specially cleaned? Were they new?

And what did it all mean?

And then the rumours began to circulate. An Important Visitor was expected, people whispered. More than just Important - a VERY Important Person altogether. No-one knew when, but strange things kept on happening. The grass in the building quadrangle was cut, and all the rubbish bins emptied twice a day. Patrols of cleaners went around picking up food wrappers and crisp packets. The windows and glass doors at the medical school entrance were cleaned and all the signs renewed. The battered chairs by the reception area were replaced by ones newly re-covered in bright floral fabric, and fresh flowers in a vase appeared on the reception desk.

Finally, it was whispered that the senior secretary had been seen coming into the building with two brand-new, especially-large, multi-coloured golf umbrellas.

And so the great day came. A convoy of chauffeur-driven Jaguars arrived, disgorging the Very Important Visitor, his assistants and his security men. A thin rain was falling, but the Very Important Visitor reached the front door without a raindrop touching him, thanks to the resourceful chief secretary and an assistant wielding multi-coloured golf umbrellas. The Important Visitor and his entourage passed rapidly down the medical school's well-lit and re-painted corridors. They stopped briefly to look at the newest refitted laboratory, where they were greeted by several senior professors wearing white coats. (When photographs of this historic occasion later appeared, everyone agreed it was the only time they had ever seen the professors wearing white coats.) After 10 minutes of photographs in the lab, the Important Personage, his retinue, and the professors proceeded to the site of a new annexe building next to the medical school. Here the Important Visitor donned a hard-hat and posed for more photographs with a ceremonial pickaxe and several important university administrators. Pausing only to tell everyone how impressed he was, the Important Visitor and his entourage returned to their cars and left.

The next day, staff entering the medical school building saw that the flowers were gone from the reception desk. On their way to the labs they passed a man in brown overalls, who was removing every other fluorescent tube from the light fittings in the main corridors. Soon life returned to normal. The floors went back to a monthly clean, the piles of undisturbed dust returned to the corners, barely visible in the half-light, and the drains smelled as bad as ever. The pictures of the Very Important Person with the Vice Chancellor and the senior Professors appeared in the university newsletter a week after the visit, but they were soon forgotten too.

Before long, people began to wonder if it had all been a dream. Some even said it had been. Apart from the new annexe building going up next door, everything in the medical school was exactly as it always had been.

Except for one thing.

In the corner of the chief secretary's office, leaning against the wall, stood an extra-large multi-coloured golf umbrella.

Mark Cain

Hirosi Kuriyama

1928 - 2003

Hirosi Kuriyama made immense contributions to our knowledge of the electrical activity of smooth muscles. For 30 years in Fukuoka until the 1990s he and members of his group produced over 500 papers on smooth muscle physiology, the responses to nerve stimulation, and the effects of new drugs on a wide variety of mammalian smooth muscles, making it the most prolific and significant smooth muscle group of that era in the world. Kuriyama published over 60 of these in *The Journal of Physiology* and was an Editor of *The Journal* from 1992 to 1999.

Young scientists from his group were visiting workers in most of the significant smooth muscle groups around the world, creating lasting links with Britain, the United States and Germany; in return there were visiting workers to the Fukuoka laboratory which included those from Slovakia (Bauer), Britain (Creed, Weston), Korea (Kim) and Germany (Isenberg, Nilius), among others. These exchanges cemented relationships among the smooth muscle fraternity and enhanced the international reputation of Kuriyama's laboratory.

Hirosi Kuriyama was born on 23 November, 1928 in Saga Prefecture, Kyushu Island of Japan, and went to university in Fukuoka where he studied medicine, obtaining his licence to practice in June 1951. After graduating he took an Assistant Professorship in the Department of Physiology, Faculty of Medicine, Kyushu University which was led by Naoki Toida. In 1956 he moved to an Associate Professorship in the Department of Physiology, Faculty of Medicine, Kagoshima University. His position there continued to 1962, although for much of the time he was abroad. Having published papers in Japanese on smooth muscle physiology in the late 1950s, he conceived the idea of working abroad to gain experience with other smooth muscle physiologists and, as he was interested in uterine smooth muscle, he first went to work in New York with Csapo in February 1959 for 15 months.

This was the era of microelectrode recording which had been used to record from the much larger skeletal muscle fibres by Ling & Gerard and others in the early 1950s, and Kuriyama and others, who were interested in smooth muscle physiology, were eager to apply the technique to that tissue. Csapo had published prolifically on the effects of oestrogen and progesterone on the mechanical and biochemical activity of uterine smooth muscle, and Kuriyama provided the electrophysiological data. The central problem which fascinated Csapo was the changes in uterine smooth muscle size and activity such that during pregnancy there were mild contractions culminating in the strong but intermittent contractions of parturition that not only expelled the fetus but also dislodged the placenta which had remained attached and functional until that time; he related these changes to the effects of the two steroids on the electrical and mechanical activity of the myometrium.

Kuriyama moved to join Edith Bülbring in Oxford in June 1960. He was to stay in Oxford until July 1964. He was a member of Lincoln College and completed a DPhil degree there. Edith Bülbring's Oxford group was at that time the Mecca of smooth muscle researchers. Previous visitors and visitors contemporary with Kuriyama in Bülbring's lab included Gustav Born, Mollie Holman, Betty Twarog, Heinz Lüllmann, Robert Lin, Richard Straub, Geoffrey Burnstock, A Crema, Johann Axelsson, C Lee, K Hermansen, Peter Goodford and Ernest Bueding – a truly international group. Kuriyama continued to publish from the Department of Pharmacology in Oxford, with Edith Bülbring until 1964, although he maintained close links after returning to Japan and made frequent visits to Britain, publishing papers with Bülbring and Tadao Tomita who joined the Oxford laboratory a little later.

While in Oxford, Kuriyama was greatly influenced by Bülbring and worked on the electrical activity of the taenia of guinea-pig caecum (called taenia coli at that time); his major contributions were the effects of changes in the ionic composition of the bathing solution, and of adrenaline and acetylcholine, on the electrical activity of taenia smooth muscle. He published with two other visitors to the Oxford laboratory, Mollie Holman (from Australia) and Rik Casteels (from Belgium); Casteels provided data on ion distributions in smooth muscle while Kuriyama recorded the electrical activity. With Holman began his interest in the responses to nerve stimulation, done at that time on the hypogastric nerve/vas deferens preparation. Later he developed an interest in the electrical syncytial nature of smooth muscle with Tadao Tomita (from Japan) who made insightful observations on the cable properties of smooth muscles independently of Mykhailo Shuba who had described them in the early 1960s in Kiev.

Kuriyama returned to Japan in July 1964 and immediately moved to the Department of Physiology at Kyushu University in Fukuoka. He was promoted to full Professor and Head of the Department of Oral Physiology, Faculty of Dentistry in 1968, transferring to become head of the Department of Pharmacology, Faculty of Medicine in 1976. He retired in 1992 from Kyushu University and, after 2 years with Chugai Pharmaceutical Company, he joined Seinan Jo Gakuin University first as Professor, then as Dean of the Faculty, and finally as President until 2003 when he was 75 years old.

Early work after returning to Japan involved studies on earthworm muscle. By the 1970s he had moved to mammalian smooth muscle, mainly

from the guinea-pig. He had many co-workers as assistants in his laboratory, many of whom are now heads of departments in Japanese universities: these included Takuro Osa (Yamaguchi, now retired), Yasuji Sakamoto (Fukuoka, retired), Hikaru Suzuki (Nagoya City) Yoshi Ito (Kyushu) Takeo Itoh (Nagoya City) and Kenji Kitamura (Fukuoka Dental College), among others. A massive number of medically qualified students passed through his laboratory over the nearly 30 years in Fukuoka, producing papers on a wide variety of aspects of smooth muscle electrophysiology, and later biochemistry and contractile processes using skinned fibres.

In his heyday between 1970 and 1990 Kuriyama's group produced the majority of electrophysiological and physiological studies which were published on smooth muscle in the era. The membrane properties of trachea, intestine, stomach, rectum, bladder, vas deferens, uterus, portal vein, and arteries such as the mesenteric, coronary, pulmonary, aorta and basilar, previously unknown, were investigated and characterised; rabbit, dog and pig tissues were investigated, in addition to guinea-pig, rat and mouse.

These studies laid the foundation for our present knowledge of smooth muscle electrophysiology upon which later voltage-clamp studies of membrane currents were able to be developed. His career spanned the period when microelectrode technique was in vogue and later tight-seal patch clamp which began in smooth muscle in the early 1980s and largely superseded it.

Studies by Kuriyama's group, and from other laboratories around the world at that time, established the basic similarities and differences of smooth muscles: voltage-dependent calcium and potassium currents acting in concert with calcium store release, complete with different combinations of receptors and innervations but with exquisite variations on a theme fitting them to perform their physiological functions in a wide variety of different situations in the body.

When invited to speak at international meetings Hirosi Kuriyama would produce copious numbers of slides, solid with membrane potential recordings or other data. During the talks he would sometimes retire to smoke his pipe outside the hall where he could be engaged in conversation. While a stern taskmaster in the laboratory, at meetings he was always relaxed, affable and approachable.

He was a council member of the Japanese Physiological Society, the Japanese Pharmacological Society, the Japan Society of Smooth Muscle Research and the Japanese Circulation Research Society. He was a member of the Physiological Society and the American Physiological Society. He was a Senator of Kyushu University and, later, of Seinan Jo Gakuin University.

Hirosi Kuriyama leaves a massive legacy of smooth muscle research, mainly electrophysiological. In his early days he was an arch exponent of microelectrode technique; he would sit by the preparation smoking his pipe, lowering the microelectrode to touch the tissue and then slightly indent it so applying a little pressure; a sharp tap with his pipe and the electrode would enter a smooth muscle cell. His practical knowledge of microelectrode technique gained during his early years enabled him to direct others using the technique very effectively and productively.

His contributions to smooth muscle electrophysiology were immense, not least in the numbers of disciples he left who now lead Japanese smooth muscle research. Internationally his group was pre-eminent in smooth muscle research for two decades; his passing marked the end of an era.

We are grateful to Ryuji Inoue for providing information for this article.

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Rob Clarke

1956 - 2004

Rob Clarke made an important contribution to physiology and to the life of the Physiological Society. An active Member since 1985, he was a regular attendee at Society Meetings where he presented more than 60 communications over the years, in his inimitable laid back style. As convenor for the Somatosensory Physiology Special Interest Group he organised numerous lively symposia during his 6 year term of office, each one invariably followed by a convivial dinner at a local hostelry, one notable occasion terminating in a game of neurophysiological charades, much to the bemusement of other patrons and, indeed, some of the participants.

In 1998 he was elected to the Committee of the Society (now the Council) where his hard work, good sense and good humour were to prove invaluable assets that won him respect and many friends. He was to have become its Chairman this year if ill health had not forced him to resign prematurely. Rob met almost every project with enthusiasm. He served on the Higher Education Sub-committee and was involved in producing a benchmarking statement with David Sanders at Newcastle. This was a pro-active move on behalf of Physiological Society and required an immense amount of work. The statement was widely used, particularly by new and overseas universities in the process of starting up physiology or physiology-related degrees and it is still available on the Society website. With others, he also helped write the booklet for schools *Understanding Life*, which gets excellent feedback from teachers and school children.

A passionate believer in the systems approach to physiology, Rob was concerned at the loss of the skills needed for integrative physiology. He led the Society's involvement in a collaborative initiative with the British Pharmacological Society to start vacation courses for undergraduate training in *in vivo* techniques. Now in their third year, these courses are running at three locations, the feedback is excellent and they are undoubtedly a positive move towards redressing a diminishing skills base.

Rob Clarke obtained a BSc in physiology at the University of Manchester in 1978 before moving go to University College London to work for his PhD with Jim Pascoe. After a post doctoral fellowship in Bruce Matthews' lab in Bristol, he accepted a lectureship in the Department of Physiology and Environmental Sciences (now Animal Sciences) at the University of Nottingham and was promoted to Senior Lecturer in 1995.

Rob was fascinated by nociceptive reflexes and how spinal processing of nociceptive information could be tempered by other nociceptive inputs that might be activated during surgical trauma or other extreme circumstances. He leaves a legacy of more than 50 papers, many published in *The Journal of Physiology*. Rob was a hands-on research scientist, never happier than in his 'lab-in-a-field' in the rural setting of the Sutton Bonington campus at Nottingham University. He was particularly excited at the prospect of taking his work forward by leaving behind the constraints of working in anaesthetised preparations and moving into the world of instrumented freely moving animals.

As well as a committed research worker, Rob was an innovative teacher who taught physiology across the board at undergraduate level. The latest edition of his textbook *Physiology at a glance*, co-authored with Jeremy Ward and Roger Linden, is due to be published in 2004 by Blackwell Publishing

Rob Clarke died in August after a lengthy battle with cancer. It is typical of Rob that he endured his ill health with stoicism and good humour and continued to work and to actively support the Society until earlier this year. Remarkably, he was even able to see a constructive side to his misfortune, once remarking how much better he felt that his lectures on pain had become as a result of personal experience. He is survived by his wife Susan and two sons.

Thelma A Lovick
Department of Physiology, University of Birmingham, Birmingham, UK

In recognition of his contribution to in vivo physiology and to the training of young physiologists, Pfizer Ltd are sponsoring a Rob Clarke Memorial Symposium to be held in conjunction with a Physiological Society meeting in 2005. Further details will be posted on the website: www.physoc.org.

Oliver Holmes

1933 – 2004

Oliver Holmes, Honorary Research Fellow in the Faculty of Biomedical and Life Sciences in the University of Glasgow since retiring as Senior Lecturer in 1998, died at home on 13 June after a short illness with rapidly progressive cancer. He had been a Member of the Physiological Society since 1961, and from 1972-76 a Committee member and Convenor of the Sub-Committee on Education and Information.

As an intercalating BSc student at University College in the 1950s, followed by an MSc as a Bayliss-Starling Scholar with GL Brown, Oliver was inspired by neurophysiology. But first he completed his medical degree and pre-registration posts. Returning to physiology, he spent a year in Liege (teaching in French!). Back in London, as an MRC Fellow with GD Dawson at the Institute of Psychiatry, he began the study of experimental epilepsy that became his life's work. He went next to Leicester as a Senior Lecturer, then as a Special Wellcome Research Fellow to the Royal Postgraduate Medical School with Professor Sir Gordon Robson and finally, in 1975, to the Institute of Physiology in Glasgow.

His investigations into the neural circuitry responsible for epilepsy involved sophisticated analysis of electrical activity in the different layers of the cerebral cortex, using anaesthetised rats with chemically induced epileptiform foci. At an early stage, he realised the need to educate himself further in mathematics, and took courses in this and in computer programming, to enable the complex cross-correlations that were required. Much later, in his 50s, he further advanced his analytical skills by taking an Open University Hons BA in mathematics.

Research-wise, Oliver was a loner among staff colleagues in Glasgow, but was rarely sole author of his many publications. A succession of PhD and Hons BSc students presented papers to the Society and published with him. Erstwhile postgraduate students testify to his inspirational influence and also to his unfailing kindness and generosity.

He also collaborated widely with clinical and academic pharmacologists, psychologists, chemists and anatomists, attracting regular grant support. He and these co-workers contributed significantly to basic epileptology. Latterly, again with grant support and in characteristically innovative fashion, he had turned to research on gastric secretion.

Oliver's teaching commitment in Glasgow was well above average not only in man-hours, but also in willingness and diligence, including organisation of courses and examinations as well as direct class contact. Modest in some contexts to the point of diffidence, Oliver could be outspoken particularly where students and teaching were concerned. An

advocate of a structured approach, he produced many series of class exercises and problem sets (long before '*PBL'!*), 'to give the students opportunities to use their physiological knowledge rather than merely to regurgitate it.' Thanks in part to his own medical education he was well able to assist understanding of any aspect of human physiology, as witness his student texts not only on human neurophysiology but also on human acid-base physiology, and publication of MCQs, spanning the whole field. He was continuing to enjoy contact with students as a 'facilitator'.

Interwoven with all this rigorous application to his work, Oliver was a devoted family man, and an accomplished 'cellist. At a summer music school in Moravia he met the Czech 'cellist, Marie, who became his wife in 1971. Of their three sons and one daughter, two now work in computing and two are medical students. Family music and pupils' concerts were a feature in the friendly family home. Oliver played with the Glasgow Chamber Orchestra. A perennial student, he enthusiastically took up musical composition in his retirement.

Oliver had no time for small talk or for socialising for its own sake, but always contributed significantly to focused discussion. Gently courteous in everyday encounters, he was a valued friend and a staunch colleague. His contribution as a physiologist and educator had by no means ended. Those of us familiar with the healthy hardy image - about town on his bicycle - and aware of his activities in 'retirement', were dismayed and deeply saddened by his rapid decline and untimely death. In Otto Hutter's words, quoted by Oliver's son at the funeral, '…in him were combined an exceptionally fine intellect, integrity of the highest order, human warmth and kindness…'

Sheila Jennett
Glasgow, UK

The Society also reports, with regret, the deaths of Michael H Harrison and Harry Berrington Stoner since the last issue of *Physiology News*.

Quantitative methods in neuroscience: a neuroanatomical approach

Edited by SM Evans, AM Janson and JR Nyengaard. 2004, Oxford University Press. 327pp, £65.00
ISBN 0-19-850528-0

Stereological techniques may yield data about the three dimensional parameters of an object, including the likely number of cells, the volume of a particular object, or its surface area and length, but sampling must be randomized to give every item of a population the same chance of being sampled. This book outlines this complex area in relation to neuroscience.

As the editors say in their General Introduction, this is 'a cookbook of stereological methods for neuroscientists', rather than a reference source for stereologists. That being said, there is a great deal of detail in each of the chapters, which may occasionally obscure the biological messages derived from the techniques, but the authors have made great efforts to keep such details to a minimum. There is an introductory chapter followed by a case study to determine neuron numbers in subpopulations of a trisomic mouse (Ts65Dn) model for Down's syndrome, using both stereology and multivariate analysis. The book then divides into five sections of unequal length (Sections 1 to 3 each have an introductory chapter to set them into context):

- section 1 – Number (5 chapters)
- section 2 – Volume (3 chapters)
- section 3 – Length and surface (3 chapters)
- section 4 – Second order stereology (1 chapter)
- section 5 – Cell culture (1 chapter).

The forms of analysis cover many areas from counting *in situ* hybridized neurons, through estimating the number and volume of immunohistochemically stained neurons in a complex brain region to estimating the length of nerve fibres and their orientation. Spatial distribution is also covered as are methods for quantifying neuron numbers and volumes in primary dissociation cultures of the hippocampus.

The book is a practical tool for the increasingly large number of neuroscientists who require specific stereological techniques. It is both informative and valuable, in that it suggests appropriate methods and statistical treatments for resolving particular types of stereological problems.

Bill Winlow

MCQs and EMQs in human physiology

6th Edition. By IC Roddie & WFM Wallace
2004, Hodder Arnold. 352 pp, £16.99
ISBN 0-340-811919

The 6th edition of this well established question and answer book provides over 3,500 opportunities for you to check that you have read the question properly and have some idea of the answer. Standard true-false MCQs form the bulk of the book, but there is also a substantial selection of extended matching answer questions (EMQs), as well as a good section of interpretative questions including graphs, tracings and tables.

In their preface the authors state that they have tried to avoid excessive detail concerning facts and figures, including some which are of value in clinical practice, but generally concentrating on conceptual aspects of physiology. They also comment that the questions are intended to cover both basic and applied aspects of the subject, but with the latter designed so that answers can be deduced by using basic physiological knowledge. Overall, the book succeeds admirably in these aims, reflecting the experience and the interest of the authors in setting clear, concise questions with valuable

learning points. The book will be of value both to those unfortunates sitting examinations in physiology and, in these busy times, to those setting them.

John A Lee

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

Long-term potentiation: enhancing neuroscience for 30 years. Edited by TVP Bliss, GL Collingridge and ROM Morris. 204, Oxford University Press. 398 pp, £65.00. ISBN 0-19-853030-7 and *Philosophical Transactions of the Royal Society* 2003, **358**, 603-842

Textbook of endocrine physiology 5e. By James E Griffin and Sergio R Ojeda. 2004, Oxford University Press. 431pp, £18.99. ISBN 0-19-516566-7

Basic and clinical neurocardiology. By Andrew J Armour and Jeffrey L Ardell. 2004, Oxford University Press. 463 pp, £50.00. ISBN 0-19-514129-6

Free radicals: enzymology, signalling and disease. Edited by C Cooper, M Wilson and V Darley Usmar. 2004, Portland Press. 230 pp, £65.00. ISBN 1-85578-161-1

NOTICEBOARD

INTERNATIONAL WORKSHOP IN ION CHANNELS

Ion channels: from physiology to pathology

Universidad de Sevilla
7-9 February, 2005

This International Workshop will focus on the general aspects of ion channel molecular physiology and channelopathies. The meeting is sponsored by the Physiological Society and intended for young scientists from the UK, Spain and Eastern European countries, though participants from other countries are also very welcome. Up to 40 applications will be accepted and preference will be given to applicants who will present a poster. Interested applicants should submit a short cv and register online by 1 September, 2004.

Website: http://www.physoc.org/international/seville2005

IUPS 2005

35th Congress of the International Union of Physiological Sciences

San Diego, CA, USA
31 March – 5 April

IUPS 2005 is being organised by the six member societies of the US National Committee of the IUPS, the American Physiological Society, the Society for Neuroscience, the Microcirculatory Society, the Society of General Physiologists, the Biomedical Engineering Society and the Society for Integrative and Comparative Biology, under the auspices of the US National Academy of Sciences.

Website: http://www.IUPS2005.org

Journal of Physiology symposia will take place at the IUPS on 4 and 5 April. Full details will be available at www.jphysiol.org

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THE MAMMALIAN MYOCARDIUM

4th International Symposium

University of Bristol
17-20 July, 2005

Further details on p. 8.

Website: http://www.bristol.ac.uk/mm2005

THE PHYSIOLOGICAL SOCIETY

Meetings 2004/2005

KING'S COLLEGE, LONDON
17-20 December, 2004 (Fri-Mon)
Joint meeting with the Chilean Physiological Society

SEVILLE, SPAIN
10-14 February, 2005 (Thu-Sat)
Sponsored symposia in association with the Spanish and Dutch Physiological Societies

IUPS/FASEB, SAN DIEGO, USA
31 March-5 April, 2005 (Thu-Tue)
(details below)

UNIVERSITY OF BRISTOL
20-23 July, 2005 (Wed-Sat)
International joint meeting of the Physiological Society and FEPS
Opening date for receipt of abstracts 1 February
Closing date for receipt of abstracts 15 March

UNIVERSITY OF OXFORD
5-7 September, 2005 (Mon-Wed)
Ion channels, genes and regulation in smooth muscle

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

Noticeboard

Notices for the Spring 2005 issue of *Physiology News* should reach the Publications Office by ..... (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.

IUPS/FASEB Meetings

31 March to 6 April, 2005 - San Diego, USA

Abstract submission deadline for IUPS is 3 November, 2004

Grants of up to £400 will be available to Members and Affiliates who are presenting at the above meeting

Information and application forms will be available from Jamie Gould (jgould@physoc.org) and on the Society's website from mid-October

Priority will be given to younger physiologists

Funds to attend this meeting will not be available from the Affiliate Grant scheme

Above: .... (left); Meetings Secretary Bridget Lumb with new Chair of the Society's Executive Committee Giovanni Mann (centre); ..... (right)

Right: Society Treasurer Jeremy Ward tries to make the figures add up (top); Mark Evans (Aberdeen) and a fireman enjoying the consequences of well-done beef (centre); Joan Mott prize winner Barbara ....

Left: ..... (top); the last vote for abstracts at the last session (centre); the fire alarm forces a mass exodus (bottom)

(Photographs by Prem Kumar and Sergey Smirnov)