PHYSIOLOGYNEWS

autumn 2005 | number 60

Oxford Meeting
Images of Bristol

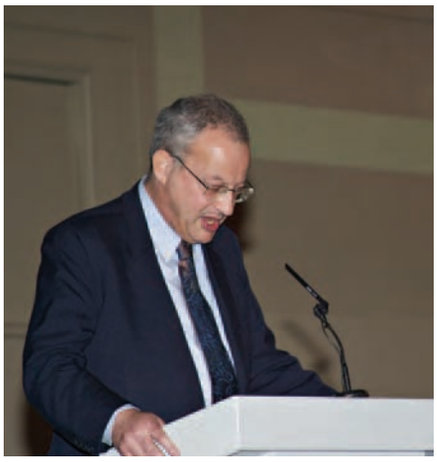
Also featuring:

A publication of The Physiological Society

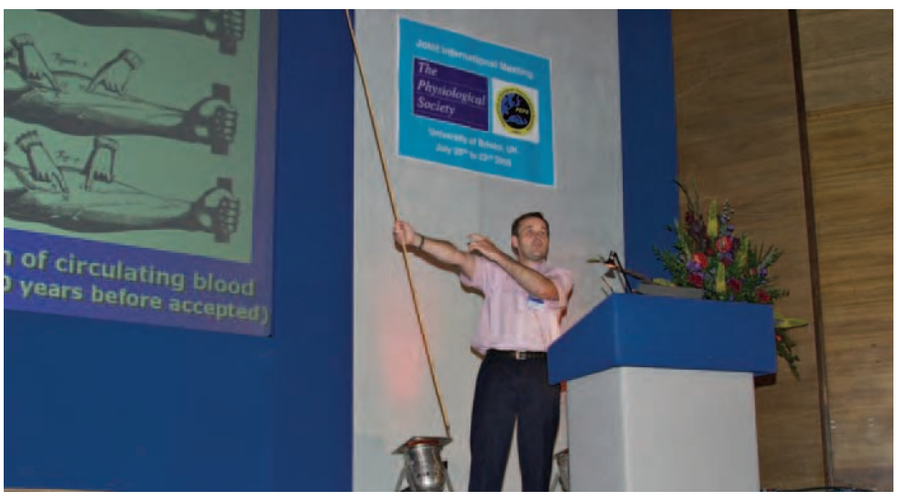
BRISTOL MEETING

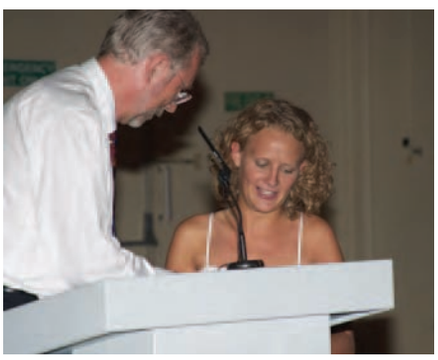
Joint International Meeting of the Physiological Society and FEPS

20-23 July 2005



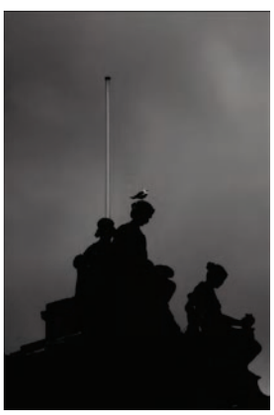
Photos include (clockwise from top left) Lord Sainsbury (Minister for Science and Innovation) speaking at the Society dinner; Pfizer Prize winner Annabel Simms with Mike Collis; retiring Treasurer Jeremy Ward; students assisting with demonstrations at the first Society Public Lecture; Julian Paton presenting the Public Lecture on *Pumping up the pressure: why high blood pressure is bad for you*.





More from Bristol in the next issue. Contributions welcome – deadline 21 September.

(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'

Published quarterly by the Physiological Society

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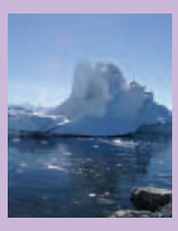
ISSN 1476-7996

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

Printed by The Lavenham Press Ltd

Cover photo



Cover illustration from *Physiology in the extreme*, p. 12

PHYSIOLOGYNEWS

Action points

Grants

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

Membership applications

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

Change of address

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

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

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Physiology News

Deadlines

Letters and articles and all other contributions for inclusion in the Winter 2005 issue, No. 61, should reach the Publications Office (lrimmer@physoc.org) by 21 September 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 the Society's web site: 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 Executive Editor.

Submission of articles

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

Illustrations and authors' photographs

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

References

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

In this issue

Welcome to the Autumn 2005 issue, which we again hope has something for everyone. A few personal selections:

In *Living History*, Roger Thomas illustrates again how the best experiments sometimes arise by a sort of series of random collisions of circumstances, and how what appears inexplicable may be the start of something interesting (p. 5). Although we should remember that, as Len Best recounts later in the issue (p. 30), the inexplicable is sometimes fated to remain just that!

Scientifically speaking we have a lot of muscle in this issue, in all its forms – smooth, cardiac and skeletal – and cover a range of aspects from control (p. 14), to excitation-contraction (pp. 17, 24, 26), to nutrient supply (p. 23). We even have both hot – or at least warm (p. 28) – and cold (p. 12) muscle.

Finally, this issue goes to press just after the Bristol Meeting, which we will be covering in depth next time. Despite the current fears for *in vivo* research in the UK (p. 39), the meeting showed that UK physiology is a thriving local scientific community with extensive global links. We like to think *Physiology News* reflects this reality.

Austin Elliott

Teaching-only – but how much?

With the outline timetable and criteria for RAE 2008 now published, the pressure is certain to mount on staff in UK university departments to produce the research papers, grants, graduate students and esteem indicators to be clearly 'RAE-ready' by the middle of 2007.

This has had, and will have, knock-on effects in many areas. One of the most profound is likely to be the complex, and sometimes vexed, relationship between teaching and research in UK universities. For biomedical scientists in universities with medical schools, there is the further wrinkle that their teaching is broadly divided into two types: teaching of departments' own degrees, for instance in physiology, and 'service' teaching of students whose degrees – medicine, dentistry, pharmacy and so on – are owned by other departments or faculties.

So how are the universities proposing to balance these competing demands on resource, and on staff time?

The emerging answer from many research-intensive institutions seems to be an increasing number of specialist teachers to reduce the teaching burden on the academic staff, with the commonest job title being 'Teaching Fellow'. Most people occupying these roles are ex-postdocs who have opted for a career path specialising in teaching, although some re-badged ex-research-active academics can also be found, especially at the senior, or at least older, end of the spectrum. Another trend visible in some places is the tendency for teaching fellows to concentrate on small-group teaching and practical classes, with the research-active academic staff taking on mostly didactic lectures and more advanced practicals.

The idea of creating teaching-only posts has historically provoked strong reactions in UK university science, with many seeing it as representing the sundering of teaching from research and the creation of a cadre of lower-paid and lower-status teaching staff. However, it has also been a stated goal of many reviews of the UK university system, and of the training of scientists, that there must be a clear career path for those whose primary interest comes to be teaching science rather than researching it.

It is undoubtedly true that currently, compared to those in traditional academic posts, teaching-only staff are more likely to be less senior, to have part-time jobs and to be on fixed-term contracts. However, a few research-intensive UK universities have instituted permanent full-time contracts for Teaching Fellows or teaching-only lecturers, and this surely must be the aim if these posts are to attract and retain the best staff. Some institutions have already set up a full career path through to Professorial-level teaching-only posts, although it is too early for many (any?) people to have actually 'trodden the road' to this level.

A potential positive aspect of the rise of Teaching Fellows is that there should now be increasing numbers of staff in the research-intensive UK universities whose job description has a clear focus on improving teaching of science subjects like physiology. It is a widely held view that, in the RAE era, academic staff under pressure to churn out papers and grants have less time to 'develop' teaching than hitherto, particularly in terms of devising new courses and lab classes for the ever-increasing number of undergraduate students. There are also other aspects of universities' missions where teaching fellows or biomedical education specialists could make a distinctive contribution. Textbook writing is one example, and another might be outreach to schools, an area where universities and learned societies have (somewhat belatedly) realised that much more needs to be done. In all these contexts the rise of teaching specialist numbers in the research-intensive universities has the potential to be a plus.

However, a nagging question is how much time people in these teaching-focused roles will actually have to do 'scholarly work', whether educational research, text-book writing, course improvement, or public engagement. In a letter to the *Times Higher Education Supplement* in July, an anonymous academic at one of the UK's less research-intensive 'new' universities stated that it was difficult, or impossible, to do anything scholarly once weekly student contact time reached 15 plus hours a week. Given the preparation, marking and associated administration, s/he argued, such jobs were in effect teaching-only, at least during university semester-time. University summer vacations once provided respite, but the increase in resit exams means that this period is now typically down to around 6 or 7 weeks, less annual holidays.

Although this accounting would probably be disputed by many academics in similar positions, it serves as a starting point. Taking the argument a step further, if teaching-only staff end up carrying 25 student contact hours per week, as the grapevine suggests is the case in some universities, when will they have time to do scholarly work? Burn-out will clearly serve no-one, and it will obviously be important for institutions creating such jobs to be clear about what the commitment in actual contact teaching hours is going to be, and what fraction of time is to be spared for other activities. The question of what the appropriate comparators are for such jobs – school teachers? Staff at US liberal arts colleges? – is one that urgently needs addressing.

It seems, then, that the Devil is in the details. The creation of Teaching Fellow posts arguably offers the possibility of renewal for science teaching and related areas in the UK's research-intensive universities, but like many new initiatives, we will probably need hindsight to see if it works. The ultimate prospects for the success of these teaching-only roles lie, I suspect, less in the job descriptions laid out for them, and more in the will of Deans and departmental heads to give the incumbents time to pursue activities other than standing in front of a class. It would be a shame if an initiative which has clear positives were to founder on the hard reality of filling slots on the timetable.

Austin Elliott

A chance to meet in Oxford and reflect on ion channels, genes and regulation in smooth muscle

This autumn will represent one of surprisingly few opportunities to focus whole-heartedly on a subject that has touched many in the fields of physiology and pharmacology over the past few decades – that of the myriad of ion channels in the myriad of smooth muscle cells throughout the mammalian body. What has been discovered? What don't we understand yet? Where is the field going? These will be questions talked about amongst the colleges of Oxford in the – hopefully – Indian summer days from 5-7 September. With generous support from the Physiological Society and British Heart Foundation the organisers will bring together 26 speakers from across the globe – 12 from the UK, the remainder from Belgium, Australia, Austria, USA, Japan, Ukraine and Canada. Particularly special amongst these guests are Tom Bolton and Alison Brading – two individuals who have shown huge commitment to the field, led it forward, inspired it and contributed seminal works over almost three decades. Tom and Alison remain engrossed in the field – we can expect more yet – but this is a chance to celebrate their contributions so far.

As a trained vet, Tom Bolton entered smooth muscle research through PhD study with the much-respected Bill Bowman. He soon showed his flare for independence and at Oxford was inspired by Edith Bülbring who pioneered electrophysiological studies of smooth muscle activity. Soon after this he obtained a position at St George's Hospital Medical School, London – a hot-bed of electrophysiology and theoretical pharmacology. He went on to head the Department of Pharmacology and Clinical Pharmacology for many years and made it a world-famous centre for smooth muscle research and a focal point for visitors from across the globe. Throughout this time he has shown us the importance of grasping hold of new developments boldly and is perhaps best recognised for his early introduction of patch-clamp recording to smooth muscle, which revolutionised the field. Patch-clamp, calcium indicators, confocal microscopy and recombinant DNA technology – all part of Tom's lab – have provided powerful tools and critical links between the smooth muscle and ion channel fields. At Oxford we will see where all of this has brought us, and what we still have to do.

Alison's research career started when she joined Peter Caldwell's lab in the Zoology Department at Bristol. It was here that her great passion for science, her remarkable insight into biological mechanisms, her broad interest and infectious enthusiasm were nurtured. Initially under Edith Bülbring's guidance, and then as an independent researcher, Alison took smooth muscle research to the next level. Her seminal discoveries included the demonstration that the action potential was carried by calcium, and not sodium ions, the importance of intracellular calcium stores in agonist-evoked contractions, the identification of Na-Ca exchange and, often overlooked, the first real evidence in smooth muscle for interaction between calcium stores and plasmalemmal calcium influx (a form of store-operated calcium entry). Alison

Oxford Department of Pharmacology, Meeting venue (above); Tom Bolton, Bo Wahlström, Edith Bülbring and Alison Brading (left to right, below) meet in Edith's Oxford office, circa 1970.

was subsequently appointed, at a very young age and in a climate dominated by male scientists, to a prestigious University Lectureship in Pharmacology with a tutorial Fellowship in Medicine at Lady Margaret Hall. Alison managed the difficult juggling act of leading an internationally acclaimed research group with a hefty collegiate and departmental teaching load superbly. However, Alison's disability due to polio (which she contracted during her gap year in sub-Saharan Africa in 1957) increased over recent years, contributing to her decision to retire a little early. Although Alison will continue to teach, her imminent retirement means Oxford is losing one of its most devoted and gifted researchers and tutors, the disciplines of physiology and pharmacology are losing one of its most eloquent advocates and we are all losing a much cherished colleague and friend.

Limited time and funds always prevent organisers from inviting everyone to speak, and on this occasion we have chosen a balance between those who worked with Alison and Tom, those who can provide an added perspective on the field, and representation from many different countries. It has been a real pleasure to see many other leading investigators also plan to join the meeting. We look set to see one of the best ever gatherings of those in the field and we hope many more of you will decide to join us and make the occasion one to inspire, drive the field forward, and also remember fondly.

Further details about the meeting can be found at http://www.physoc.org/meetings/

David Beech, Anant Parekh and Phil Aaronson
Meeting Organisers

How I came to probe intracellular pH and realised it can be interesting

I came to pH via the sodium pump. In 1967 I was working as a postdoc in EJ Harris's (Fig. 1) lab in the Biophysics Department of University College London. I was trying to prove that the current generated by the sodium pump in snail neurones was proportional to pump activity. One way to show this would be to measure changes in $[Na^+]_i$ with a Na^+-sensitive microelectrode. Joe Hinke had been a postdoc in UCL when he first measured Na^+ and K^+ in squid axons with glass ion-sensitive microelectrodes (Hinke, 1959). His design (Fig. 2A) had an exposed tip of sensitive glass protruding from the end of an insulating glass micropipette, and was suitable only for very large cells. Alas, a search of the department's cupboards revealed no left-over glass. I therefore wrote a begging letter to Corning Glass in New York, and was lucky to obtain some of the special glass as a gift from Corning's glass chemist Normand Hebert. I spent a long time failing to make different shapes, advised by fellow post-docs such as Enrico Stefani (see Fig. 3) until, in the middle of 1968, I successfully made electrodes with the new reversed-tip design (Fig. 2B and Fig. 4A). Only the (admittedly large) tip had to cross the cell membrane, while with Hinke's design the whole exposed length of ion-sensitive glass must be inside the cell. Once I had succeeded in doing a few convincing experiments with these reverse-tipped electrodes on the largest neurones in the snail brain, I wrote to tell Normand Hebert, who invited me to visit Corning when next in the USA.

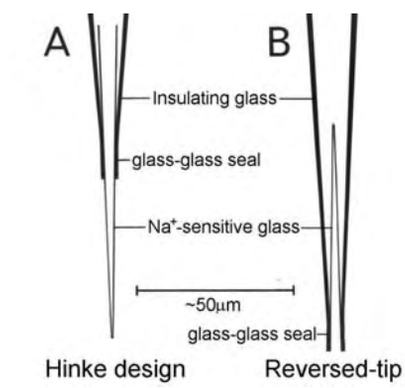


Figure 1 (top). EJ Harris, photographed in Philadelphia holding *Playboy* magazine in 1966, in whose lab at UCL I first made Na^+-sensitive microelectrodes. He was always known only as 'EJ'. **Figure 2** (above). Diagram showing tips of two designs of Na^+-sensitive microelectrode.

By this time EJ had decided that I had done more than enough with neurones, and with help from the Head of Department persuaded me to agree to work on a project of EJ's choice, as soon as I had written up the sodium pump work. EJ nobly refused to allow me to put his name as co-author of this paper (Thomas, 1969). I finished the manuscript in the summer of 1968, somehow including nothing in the Methods section about how I had calibrated the Na^+-sensitive electrodes. The referees did not notice. I later described my results in my first ever Physiological Society Communication, at the December 1968 meeting in Leicester, but did not request publication since the full paper had just been accepted.

Figure 3. Roger Thomas and Enrico Stefani as post-docs in the Biophysics Department of UCL in 1968.

I and my wife duly spent a few weeks in the USA that September. My first postdoc job had been in New York City from 1964-66, so we stayed with friends there. Between visits to various physiologists, I flew up to Corning, the company town in New York State. As I recall, the Corning Research labs were flying the Union Flag over their entrance when I arrived. Normand Hebert (Fig. 5) claimed this was in honour of my visit, but I only half believed him! At the end of my visit Normand pressed upon me not only generous amounts of Na^+-sensitive glass (hundreds of pounds-worth), but also a large quantity of pH-sensitive 1 mm glass tubing, despite my protests that I was not interested in pH. This turned out to be a career-changing gift.

For my last year at UCL I worked with EJ on Ca^{2+} uptake by rat liver mitochondria. I made small glass pH and K^+ electrodes, and using these as well as the Ca^{2+}-indicator murexide to measure external Ca^{2+} we showed that anoxic mitochondria would take up Ca^{2+} ions and extrude H^+ when given oxygen (Thomas *et al*. 1969). I confess I was overall not a very useful postdoc, and I fear EJ never forgave me for what he saw as the two wasted years I spent on the sodium pump.

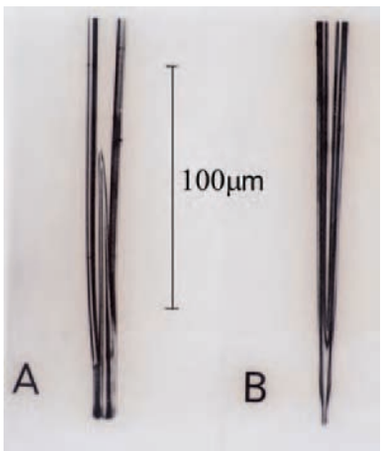
When I was appointed by Arthur Buller (Fig. 6) to a lectureship in physiology in Bristol in 1969, I resolved to resume working on the sodium pump in snail neurones and make a better Na^+-sensitive microelectrode. Better, that is, than the 8-10 micron-tipped ones I had used earlier. As part of my start-up

allocation, I had a Faraday Cage built in Lowestoft, which I still use, and bought a Keithley vibrating-capacitor electrometer. I remember that the latter cost the huge sum of £1,600, roughly the same as my annual salary, but was the best amplifier available for recording DC voltages from ion-sensitive microelectrodes, which have resistances of up to 10^{11} ohms. The amplifier head stage can be seen at the back of the photograph of my setup (Fig. 7), which was completed by four Prior micromanipulators (donated by Arthur Buller), a snail brain bath, various custom-made amplifiers and a current clamp of my own design. The red-handled hand lens used to focus light on the snail brain had been bought in the Tottenham Court Road Woolworths, for, I recall, 2s 6d (12.5p).

My new design for a sharper Na^+-sensitive microelectrode had been suggested during the lunchtime discussions at UCL, but had proved impossible to make there. After much trial and error in Bristol, I found it relatively straightforward to make 'recessed-tip' microelectrodes as shown in Figs. 3C and 4B. They were made by heat-sealing the outer borosilicate glass to the inner Na^+-sensitive glass. This was possible because the inner glass had a higher melting point than borosilicate glass. Only the relatively small tip (about 1µm) needed to cross the cell membrane, as shown in Fig. 8. I demonstrated this new design to the Physiological Society in July 1970, did more experiments on the sodium pump and wrote a review (Thomas, 1972).

By 1972 I had two PhD students, Tim Neild and Richard Vaughan-Jones (Figs. 9 and 10) and had grown my hair much longer (Fig. 11). I spent a lot of time trying to make recessed-tip Cl^--sensitive microelectrodes with Tim, and Na^+- sensitive microelectrodes with Richard. Tim recalls he used to horrify us by generating strong odours of cyanide, which he could not smell, while etching silver wires. Visitors to the department to whom I showed the Na^+-sensitive electrodes kept asking whether I could perhaps make similar pH-sensitive ones. Having plenty of pH-sensitive glass in my drawer, these challenges eventually led me, sometime in late 1972, to work out how. Richard has reminded me that a glass chemist I consulted doubted that it was possible to properly seal glasses with such different coefficients of expansion as pH-sensitive and borosilicate glass. When I tried the method which worked for Na^+-sensitive glass, the pH glass simply melted into a solid mass.

The procedure I eventually devised was to apply air pressure from a plastic syringe, later a gas cylinder, to the inside of the previously-sealed pH micropipette while softening the glass with heat from a platinum wire loop. (Fig. 12; see also Thomas 1978). Amazingly, no cracks formed as the glass cooled, except above the blown area. These electrodes were insensitive at first, but after soaking in water for about 3 weeks (I nearly threw them



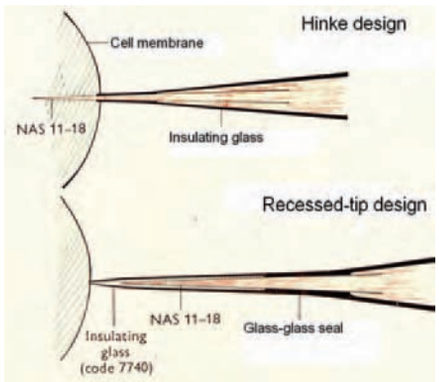


Figure 4 (top left). Photographs of Na^+-sensitive glass microelectrodes. A, Reversed-tip; B, Recessed-tip. **Figure 5** (centre, left). Normand Hebert photographed in 1968. **Figure 6** (left). Arthur J Buller, Head of Department of Physiology, University of Bristol, from 1965-75. **Figure 8** (top, right). Diagram showing how deep the electrodes must be inserted. **Figure 9** (centre, right). Tim Neild, my first research student, in 1974. **Figure 10** (above). Richard Vaughan-Jones, my second research student, also photographed in 1974. Richard is the tall one in the middle.

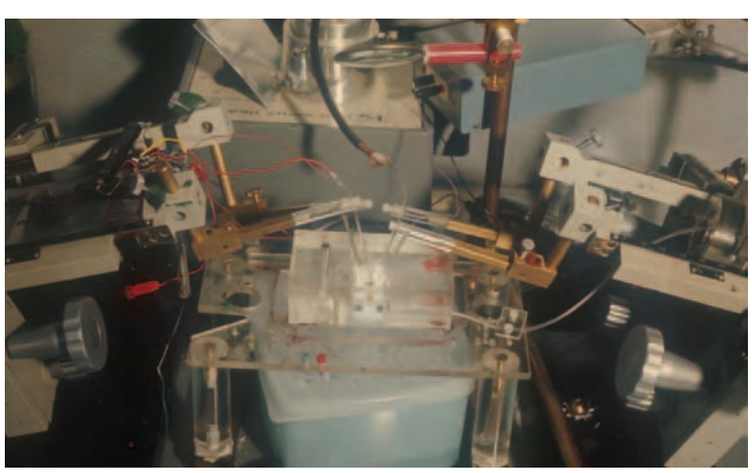


Figure 7. My experimental bath and microelectrode setup in about 1973.

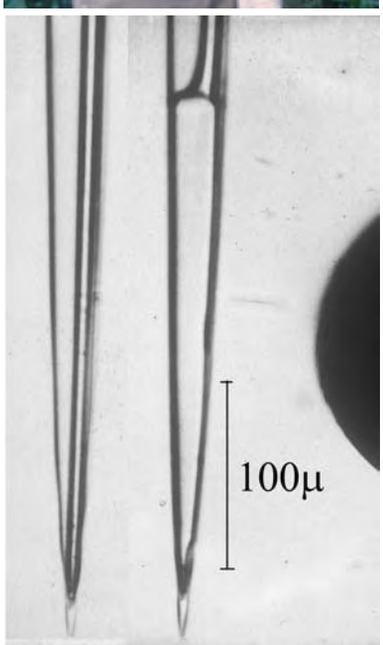


Figure 11 (top). Roger Thomas with son Daniel in 1972. **Figure 12** (above). The sharp end of a recessed-tip pH-sensitive microelectrode, before and after heating by a loop of platinum wire. The tip of the heating loop can be seen on the right. Note that the inner pH-sensitive glass has been blown outwards to seal to the inside of the outer micropipette.
Figure 13 (right). Figure made in 2005 from a pen-recording made on 29 January 1974. I used four microelectrodes: in order of insertion into the snail neurone they were pH-sensitive, KCl-filled for potential, KCl-filled for return current, and NH_4HCO_3–filled for injection. About 40 min from the start I began to load the cell with acid by iontophoretically injecting NH_4^+ ions. Inside the cell the NH_4^+ became H^+ and NH_3; the latter leaving the cell easily since it is uncharged. Once pH_i had reached about 6.7, I briefly switched the perfusate from CO_2-free to one with CO_2 and bicarbonate. This caused a brief fall as CO_2 entered then a rapid increase in pH_i, though I was still injecting NH_4^+ ions. When I switched back to CO_2-free Ringer, pH_i returned towards 6.7. Note that the pen-recorder had a very slow response, so that action potentials were much reduced in size.

(Photos 1-9, 11 and 12 by Roger Thomas. Figure 10 by Monica Thomas)

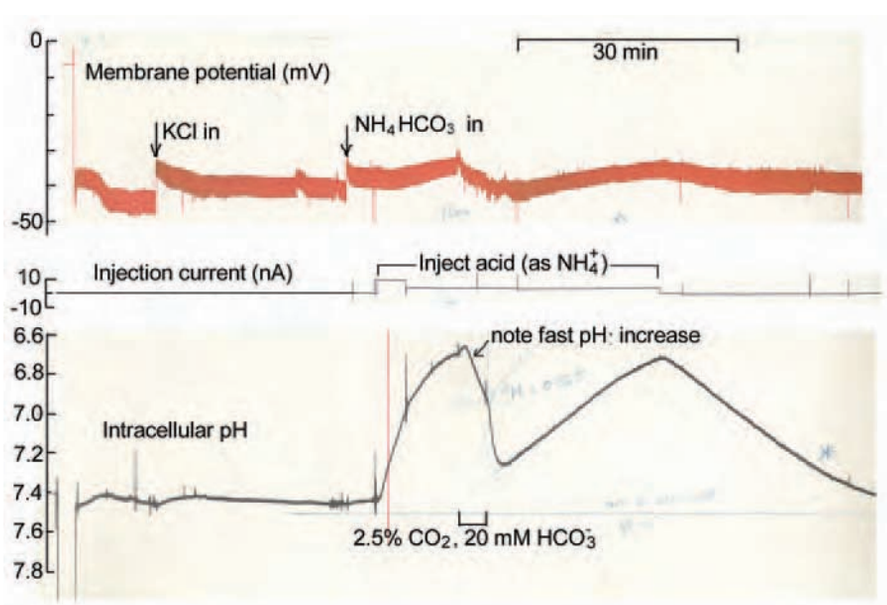
away before discovering this) they seemed to record pH_i quite well, although they were inherently rather slow to respond to changes. (By one of those coincidences it's hard to believe, one of my holiday jobs while an undergraduate had been in the Analytical Chemistry section at Pye Instruments in Cambridge, where I helped with customer complaints of faulty pH electrodes. Often the electrodes were revived by prolonged soaking.)

I thought I really ought to prove that my recessed pH-sensitive microelectrodes worked intracellularly, rather than simply reporting success in making them, so I did a variety of experiments with snail ganglia bathed in normal CO_2-free snail Ringer and wrote a paper about them in late 1973 (Thomas, 1974). I am now horrified how little I then understood my results. I was particularly impressed by the speed with which pH_i changed when I added CO_2 or ammonia, but completely failed to appreciate that bicarbonate accelerated the rate of recovery from acidification. My estimates of buffering power were very careless too. But my main conclusion was valid: the recessed-tip design gave an accurate and direct reading of intracellular pH.

It was not until January 1974 that I began to suspect that pH_i was regulated very much faster in CO_2/bicarbonate buffered than in CO_2-free solutions. I show here for the first time part of the experiment that made me begin to realise that bicarbonate greatly stimulated pH_i recovery from an acid load (Fig. 13). When I then switched to bicarbonate Ringer, I was surprised to see that pH_i began to increase rapidly, although I had not changed the external pH. It was around this time that I realized that very little was known about intracellular pH homeostasis, and that it really was of great physiological importance. I wrote on the pen-recorder paper 'Get strong impression that H^+ pump greatly stim. by CO_2/bicarbonate. The OH^- pump (or reverse H^+ pump) seems much slower.' A few months later I added 'OR Bicarb increases Buff. Power.'

Of course, I now know bicarbonate does both. I decided to work on buffering before returning to the pump, but foolishly (Richard Vaughan-Jones reminds me) failed to read the chapter by Woodbury (1965) in Ruch & Patton's textbook which explained the theory of open buffering systems. Meanwhile Walter Boron in St Louis started to work with Paul De Weer on pH in squid giant axons, using Hinke-style electrodes.

So the two most important reasons for my leap into the little known world of intracellular pH were Normand Hebert's (and Corning's) generosity, and persistent questions by visitors to the department. Without these 'prompts' I



might never have bothered. My work was supported by grants from the MRC to study the sodium pump, but I did later get money from them to study pH! I am very grateful to them and to Arthur Buller and the University of Bristol for their generous support over many years.

Roger C Thomas
Physiological Laboratory, University of Cambridge, UK

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Where are they now?

EJ Harris seems to have retired in the 70s to devote more time to his collections of early English silver coins, but is now more concerned with local archaeology. He still lives in Kenton.

Enrico Stefani is Professor of Anesthesiology and Physiology at UCLA, Los Angeles.

Normand Hebert left Corning to set up Microelectrodes Inc which is still operating in New Hampshire selling various mini and microelectrodes.

Arthur Buller is living in retirement in West Sussex.

Tim Neild is Associate Dean of Teaching and Learning for the Faculty of Health Sciences of Flinders University, Adelaide, Australia, and an expert in Problem-Based Learning.

Richard Vaughan-Jones is University Professor of Cellular Physiology, Oxford, and leads the Proton Transport Group.

Roger Thomas was Head of the Physiology Department of the University of Cambridge at the time of writing. By the publication date he expects to be the 1883 Professor of Physiology in the Department of Anatomy and Physiology.

Letter from ... Nigeria

Frank Mojiminiyi

It is likely that the first set of Nigerians to be exposed to the formal learning of physiology as a subject are those that first graduated in medicine. If that is so, then the honour goes to the duo of William B Davies and James Africanus B Horton, who graduated in medicine from King's College London in 1858 (Adeloye, 1985). In 1930 the Yaba Medical School was established in Lagos. It granted diplomas and certificates in selected medical subjects. Physiology was probably among the subjects taught to her students. However, physiology was introduced unequivocally into Nigeria in 1948, when the British colonial government opened University College Ibadan in affiliation with the University of London. The basic medical sciences, including physiology, were taught at Ibadan while the clinical training was concluded in London. In the 1960s, after independence from Britain, four other universities with medical schools (at Nsukka, Lagos, Zaria and Ife) were added. Initially, only medical doctors were trained. Later a BSc programme in physiology was added in Ibadan and Lagos. Some of the graduates from these institutions later travelled, mostly to Britain, and to some extent Europe or America, to obtain postgraduate training in physiology.

Today, there are about 21 medical schools in Nigeria, each with a department of physiology. Six of these run a BSc programme in physiology, and six also have postgraduate programmes in physiology. Of the latter six departments, two have received support from the Physiological Society, namely the laboratories headed by Soga Sofola in Lagos and Tony Ebeigbe in Benin. This support placed these laboratories in a better position to offer postgraduate training in vascular biology. I did my PhD under the tutelage of Soga Sofola. Therefore, I may be regarded as one of the beneficiaries of the largess of the Physiological Society as well as other organizations that supported this laboratory by way of grants.

Physiological research in Nigeria is wide ranging, with each department addressing problems it considers important. My own department is at the Usman DanFodio University Sokoto, in the far north of Nigeria. One group in my department is focusing on vascular mechanisms of salt-sensitive hypertension using albino rats fed an excess salt diet. Most hypertensive patients in Nigeria are salt-sensitive. Their work also involves validation of a plethora of herbs used by native doctors for the treatment of hypertension. The long term goal of this team is to develop an antihypertensive drug from these herbs. Another group is studying thirst and thirst mechanisms. As the temperature in Sokoto reaches a peak of about 45°C in the dry season, thirst is a big problem.

Regardless of what research is embarked upon, one problem confronting physiologists in Nigeria is the inadequate supply of laboratory equipment, chemicals and reagents. This is a direct consequence of underfunding, and makes it difficult to address a problem consistently and pursue it to its logical conclusion.

Underfunding is multifaceted. Among its contending factors are governmental apathy and lip service to education, corruption, a looming foreign debt and scandalous devalutation of the Naira (Nigerian currency), making the prices of imported items out of this world! Since all scientific equipment, chemicals and reagents are imported, their cost is prohibitive.

Fortunately, with the advent of democracy, there appears to be a chink of light at the end of the tunnel and funding has improved somewhat. For instance, there is now a quarterly governmental grant, Direct Teaching and Laboratory Costs (DTLC), which is directly available to each department for the purchase of reagents and consumables. Also, each department has been requested to submit a list of equipment for purchase by the government, and the civilian government *appears* to be having an unprecedented and titanic clash with the demon, corruption. At the last count several people have been axed, including the Senate president (number three in hierarchy from the President), the Minister of Education and some high profile members of the National Assembly (Parliament) as a result of a bribery scam in the educational sector. And the icing on the cake? The Paris Club of Banks decided to write off 60% of the national debt! It is hoped that this will transform into a greater and more robust funding of education. Nigerians were ecstatic. It was hailed as *the* dividend of democracy! But, alas, the euphoria was not to last long – coming very closely after the announcement of the debt write-off was the mindless terrorist bombing of London in July.

In spite of the strides taken above, physiologists in Nigeria still need help.

We are gratified by the mission statement of the Physiological Society which is: '*to promote for the benefit of the public the advancement of Physiology, and facilitate the intercourse of Physiologists, both at home* ***and abroad'***. Indeed it was this statement that spurred me to apply for the Society's Centres of Excellence Support scheme on behalf of my department. This scheme would have enabled us to purchase equipment that would have given a fillip to our work, but we were not eligible. Instead I was invited as a foreign guest to the King's Meeting, which was good too (see *Physiology News*, **59**, 13)!

In spite of the daunting conditions under which we have to work, physiologists in Nigeria have managed to forge ahead. Our umbrella body is the Physiological Society of Nigeria. The Society holds a scientific conference once a year. To my mind, the quality of work presented at these conferences is good, as evidenced by the acceptance of some of them for publication in international peer review journals. Abstracts of these works appear in the post-conference issue of the Society's journal, *The Nigerian Journal of Physiological Sciences*. This year the Physiological Society of Nigeria will be 25. The silver jubilee celebrations and XXVth annual scientific conference will be hosted by the Department of Physiology, University of Port-Harcourt in the oil-rich Niger delta. The theme of the conference is *The effects of environmental assaults on human physiology.* It will take place from 15-16 September 2005 and will bring to the front burner the effects of oil spillages and oil pollution resulting from the unwholesome practices of the multinationals drilling oil in the Niger delta!

Academic procession at Nigeria's University of Ibadan (above). The Trenchard halls of residence, University of Ibadan (top)

Acknowledgements

Many thanks to Lucilla Poston for her consistent support for physiology in Nigeria over the years. We are also grateful to Terence Bennett for the lifeline to our department by way of equipment supply, to Jeremy Ward, David Eisner and Helen Close.

Frank Mojiminiyi

Department of Physiology, College of Health Sciences, Usman DanFodio University, Sokoto, Nigeria

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(Almost) a week in the life of an IUPS delegate

Peter Brown spends 88 hours in San Diego and reflects on a meeting that was all positive and threatened to swamp *Experimental Biology*

Saturday

Arrive in San Diego appropriately jet-lagged after 16 hour journey. Another one of those 'good news ... bad news' scenarios. The good news: an upgrade to business class on the transatlantic leg – only my 2nd upgrade in 25-odd years of air travel. The bad news: on arrival in Atlanta, rumours of shoe X-rays, strip searches and 4 hour lines at the airport prove only slightly exaggerated. After 90 min wait at Immigration miss connecting flight to San Diego and arrive cursing 3 hours late.

(It could have been worse, though. I later find out about a Manchester colleague who found the US visa procedure so convoluted and time-consuming that, when it emerged the only way to get a visa would be to turn up at the US Embassy in London at 7 a.m. and stand in a 5 hour queue, he simply gave up. The whole thing makes me rather doubtful about 'biometric passports' and ID cards, but that's another story).

Sunday

Emerge jet-lagged and struggle down to registration. I did mean to get here for the 8 a.m. talks (honestly), but by the

time I have navigated my way around the conference centre a couple of times to reach registration, abstract book collection etc. etc. I find my first talk is in David Sheppard's 10.30 a.m. session on *The Molecular Basis of Epithelial Disease*. As with all the sessions I check out during the meeting, the talks are nicely presented and well-attended. Pity a few more Brits hadn't made the effort to be here, though.

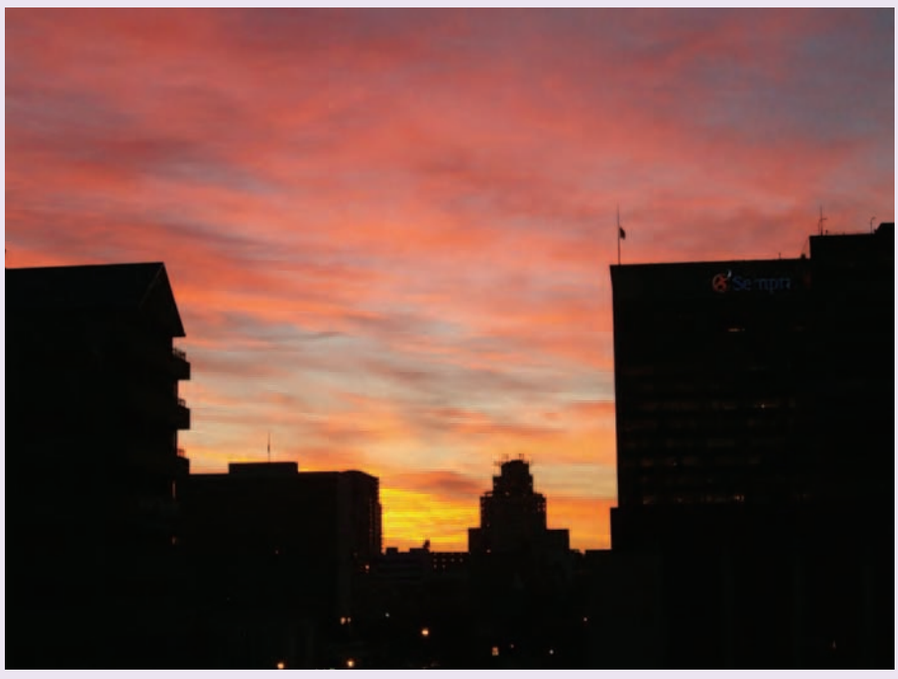
Sunday evening meal out with some friends from my LA days – a curry. Eating out in Southern California has a lot of good points, including restaurants with terraces overlooking the sea and the climate to make use of them, but they still don't seem to have got the hang of cooking a really decent curry. When it comes to chicken Dhansak, South Manchester beats Southern California every time.

Monday

Browse round the poster session. San Diego's evening attractions have been keeping some of the delegates busy and a few look pretty shaky today. One colleague (name deleted in return for a mixed case of wine) appears late, looking particularly pale. He defends himself by claiming his attendance is, in fact, an example of heroic endurance – apparently the people he was partying with last night haven't made it to present their posters at all. Score one for the British constitution. No, not that British constitution, the other one.

At the coffee break, a friend who has been meeting non-science acquaintances in San Diego tells me he has witnessed a key West Coast ritual – 'waiting for the green flash'. To experience this, you stand on the beach staring out to the Pacific and watch the sun go right down. The idea is that, as it dips completely below the horizon, the last sunlight is shining through water to reach the observer and it looks like a flash of green light. My informant swears there were several dozen people standing waiting, many of whom were veteran flash-watchers, and insists he heard one surfer type say: 'Totally awesome flash, dude'. Decide he has been watching too many episodes of The OC.

For someone who spent 2 years in LA as a postdoc in the 1980s, and has holidayed in California several times, this surprisingly is my first visit to San Diego. To be honest, no-one in LA ever mentioned the place: San Francisco, Yosemite, Death Valley, King's



Peter Brown (above). San Diego – sunset over the downtown hotels (left)

Canyon, Monterey… but never San Diego! My first impressions are that, while maybe not the most exciting place in the world, it is well-appointed for a large conference: excellent conference centre (center?), plenty of bars, restaurants and hotels all within walking distance, and a wonderful climate.

San Diego also seems to celebrate its Spanish/Mexican heritage more than LA although, of course, parts of LA are heavily Spanish-influenced. I particularly remember going to the wedding of an English friend of mine called Nigel in Downtown LA in the 80s, where the official in charge insisted on calling him 'Miguel' throughout the ceremony! Although, on reflection, that tells you more about how few Nigels there are in the US than about anything else. Anyway, the Mexican-American cuisine here is first-rate, and I sample it a couple of times during the meeting.

Tuesday

The day of the symposium I am co-organising. Have never quite figured out the etiquette of being a symposium organiser. The million dollar question: to be a speaker – or not to be?

I was always taught not to invite myself to speak, on the basis that it makes you look self-important. On the other hand, a former Head of Department of mine once told me firmly that I was a fool NOT to be a speaker in any symposium I was organising. 'Get those b*!*dy Esteem Indicators stacked up', he said. 'If you don't think you're good enough, who the *!!* else will?' Have reached a personal compromise solution – speaker last time I was organiser, chairman (but not speaker) this time. The symposium draws a decent audience of around 60 or so – not bad for the final day of a meeting.

Having missed a big chunk of the meeting it is difficult to say what the highlights were, but I get the feeling that the organisers have saved the best for last: *The Journal of Physiology*-sponsored session on *TRP channels* on Tuesday afternoon is excellent for the most part: innovative sciences with well-paced and witty presentations.

Wednesday

Take-off at lunchtime. Have been here exactly 88 hours. Since the journey out here took 16 hours, and the journey back will be another 12, this means a stay-to-transit time ratio of 3.14. Shouldn't complain about this, though – my choice.

Like most people, I used to take more extended conference trips when I was in my 20s and early 30s, with no family to get back to and a budget that didn't stretch to long-haul holidays other than ones that were 'conference-assisted'. But these last few years 4-5 days is my usual limit. There is a tricky balancing act to accomplish here, though.

I remember sniggering at one (now ex-) Manchester professor who told me he flew annually to Florida for only 2 days for a high-powered American meeting and had mastered the routine. 'I've figured out how to beat the jet-lag', he said. 'What I do is stay in the lecture theatres all day, never go out in the daylight, and go to bed straight after supper. That way I can stay on UK time and never start to adapt. And it means I wake up at 4 a.m. so I have lots of time to read the abstract book'. I tell myself that, as long as my stay-to-transit time ratio never gets below 2.0, I can keep believing I haven't reached that point.

The flight home gives time to reflect on some general points about the meeting – all positive. The organisation was good, as was the science. I don't usually like huge meetings, but any fears that IUPS would be swamped by Experimental Biology/FASEB failed to materialise. If anything, IUPS seemed to be swamping EB! Finally, it was great to see that many of the 'Big Players' in structure-function have returned to their physiological roots and want to study the function of proteins in real cells/organs/animals.

Thursday

9 a.m. Manchester time - touch-down. Good to be home, though the drizzle provokes a slight lingering hankering for California sun! May see you in Kyoto for IUPS 2009…

Peter Brown
University of Manchester, UK

LETTER TO THE EDITOR

Keeping it accurate

I very strongly agree with your recent editorial *Keeping it accurate* (*Physiology News* **57**, 3). Surely editorial boards and editors of scientific journals have an important role here. Article titles increasingly emphasise the main results of a study. This makes the life of those scanning for publications of interest easier but does require a balance to avoid contributing to the climate of spin you rightly decry.

The time has come when editors should demand a section in every paper on 'weaknesses in the study' to add to introduction, methods, results and discussion. Such a weaknesses section should be not merely in the body but also in the summary of every paper ... and, of course, every press release spun off from the article.

You are correct: 'might' is an important word. Let's give it its full weight. Let us emphasise the basis for that 'might'.

Sir Robert Boyd
University of Manchester, UK

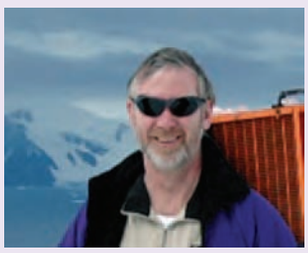
New Chief Executive for the Biosciences Federation

Dr Richard Dyer has been appointed as the new Chief Executive of the Biosciences Federation to replace Mike Withnall when he retires at the end of the year. Dr Dyer is widely recognized to have done an excellent job as Director of the Babraham Institute and will bring considerable enthusiasm as well as valuable experience of leading and managing a large organization. President Sir Tom Blundell commented 'The biosciences are in a period of rapid and revolutionary discovery and growth, with many implications for Government and the public, as well as for bioscientists themselves. With his background of outstanding science and proven leadership, Richard Dyer is an impressive appointment as Chief Executive. He will ensure a strong future for the Biosciences Federation and make a major contribution to the health of bioscience in the UK'.

(See Mike Withnall's update on the activities of the Biosciences Federation on p. 44.)

Physiology in the extreme

What drives perfectly sane physiologists to leave the comfort of their home labs to travel across the world to hostile environments in pursuit of their particular holy grail? By day Stuart Egginton is a Reader in Cardiovascular Physiology at the University of Birmingham, living the sort of academic existence that most of us would recognise. But from time to time he ups sticks and takes off for Antarctica. Thelma Lovick tries to find out why



Stuart Egginton

Thelma Lovick (TL) Why go all that way just to study the antics of some Antarctic fish?

Stuart Egginton (SE) You can do there what you can't do here. We have access to animals that are not found anywhere else, because the Southern Ocean is bounded by the polar front which physically separates them from the rest of the planet. This is a unique situation in a marine environment. If you want to look at low temperature physiology, there are vertebrates in Antarctica that have the lowest core temperature of all – about -2ºC during their active lifestyle.

But the real drive is that you have access to a genetically closely related group of animals in a stable environment. So any comparative study avoids the confounding variance of almost any other system. As a physiologist this allows me to specifically explore phenotypic plasticity. What we have there is the aquatic equivalent of Darwin's finches at low temperature. In addition, as we have the detailed geological record, we know we're looking at evolution in progress.

TL So does that put what you're doing in the same league as Darwin?

SE Well of course I'd like to think so, but I'm more of a realist! Let's just say, we are finding out things that are unique, which is really exciting.

TL What's it like doing science in such an extreme environment?

SE Even the logistics of getting there and existing there can be quite challenging. You only have access to the research bases during the Austral summer, which is about 3-4 months long. This is when ships and aircraft can get access to the land avoiding the frozen sea. Even so there's no guarantee of actually getting there. Out of six attempted trips, I failed twice to make it. Once the boat I was on got stuck in pack ice and the second time I was recalled for family reasons – very frustrating. The temperature varies from -10ºC to about +2ºC on a fine summer day. But, of course, the further south you get, the shorter the 'night', which in reality is only twilight. I rarely ever adjust to the light schedule and consequently tend to have very long days and end up sleep-deprived. Usually I get up early, make some breakfast in the galley and then head into the lab. There are set mealtimes for lunch and dinner with 'smoko' breaks in between. This routine is left over from the naval origins of the British Antarctic Survey. So basically we follow the same pattern that Scott did.

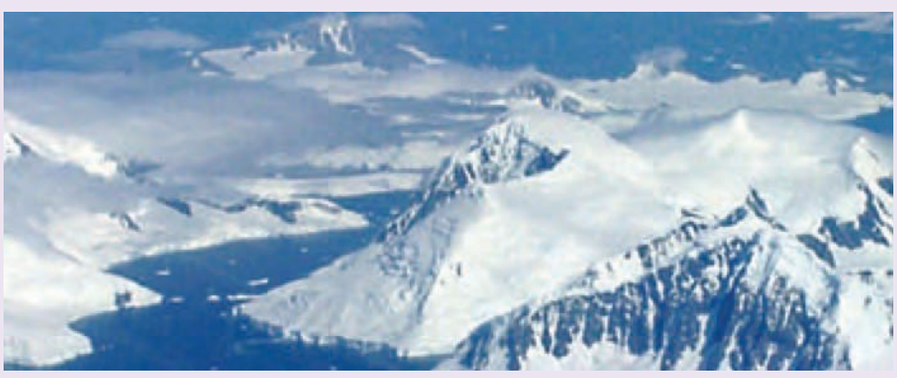
Antarctica – where science is cool...

TL What are the worst bits about working in the freezing cold?

SE When you start doing surgery, your fingers are in sub- zero water, so manual dexterity becomes a challenge. There comes a point when your free nerve endings are screaming at you to get out of the cold. So you warm your hands under a hot air fan and almost immediately you regret it because you have micro-abrasions on your skin due to the fish's teeth or spines. And as you warm up and salt water enters the cuts…these are the times when it doesn't seem to be such a good idea to be there.

TL Do you ever find you've left that essential key bit of kit at home?

SE You have to develop the mentality to pack up a complete lab and take it all with you. Everything you take into the base you take out. And that includes all your bodily wastes. We can't afford any pollution of the environment - this is not Everest! So usually I pack the resources to do probably three projects, on the assumption that at least one isn't going to work. You can't rely on any spare parts or any equipment being available. It can mean a lot of down time in the lab at home beforehand, because a lot of equipment has to be shipped south 3 months before you arrive on the base. When you get there, it really is a one man operation. And, of course, there's no animal house. It certainly teaches you to be economical with numbers when you have to go out and catch your experimental animals



first, especially on small boats in a 20ft swell and freezing spray!

TL How many people are on the base?

SE Usually 24 over the winter, but probably about 120 or so go through during the summer. So at any one time there are 60-80 people there. There are base support people who run the aircraft, boats, etc. and then the physical scientists who go out to do atmospherics or glacial work and the biologists who try and examine adaptations to probably the most extreme environment in the planet.

TL This sounds like a very intense environment where you are probably fairly short of personal space. What's the social scene like down there? What do you do when you're not working?

'Great God this is an awful place' (Captain R F Scott)

SE The maritime environment gives you wind, sleet, grey skies – in fact miserable conditions for 80% of the time. When you're walking across to main base for your meal and you can hardly see 10ft in front of you, the words of Scott come to mind: 'Great God, this is an awful place'.

When the sun shines, though, it is pure magic. You have options of skiing, snowboarding on the glacier, walking around the shoreline taking photos of wildlife and, if you are very fortunate, you get to act as co-pilot on one of the Twin Otters that fly out to supply the field operations, or to go on the small boats to support the diving or sample collection.

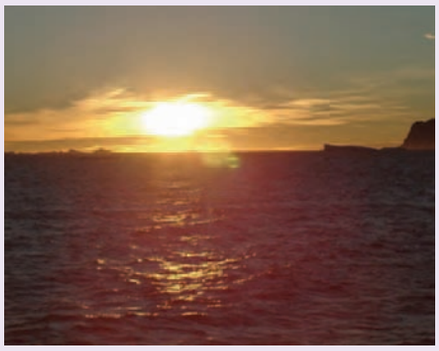
You have to constantly concentrate on the environment, though, and not get lulled into a false sense of security. The conditions can change frighteningly fast. Memorial plaques to many who have lost their lives in the pursuit of science down there are a harsh reminder of the unforgiving nature of an environment where your first mistake may be your last. In fact, all visitors now have to undergo training to make sure you could survive should disaster strike, as it did 3 years ago when the Bonner lab burnt down. There are primitive huts dotted around and these can actually provide a welcome refuge for a day or so to let you get your head back together if cabin fever strikes!

...an environment where your first mistake may be your last

TL Do you really manage to leave behind all the day-to-day irritations that, increasingly, come with the territory of being a university academic?

SE When I first went down we had an allocation of 200 words per month by telex. This mode of communication was difficult for personal contact, especially with a wife and 9 month old baby, as he then was. Despite that, and being 8,500 miles away from my notes, I still got a telex demanding exam questions! Now we have email, and I have to say that the delete button gets a lot of use. Just this year, we got a high-bandwidth satellite link, so we now have web access and telephone access, when atmospheric conditions permit.

There's also lot of interest shown by the public in what goes on at the base so quite a lot of time is spent answering requests for interviews from TV, radio and print media. Our current project made it on to the BBC and Sky news recently. The public like the idea of remote science. It's a photogenic environment, you can link it with global warming, and there is a tenuous link with medical advances in fields like hypothermia and the use of cryprotection in transplanting organs.



TL Finally, is all this trouble really worth it?

SE Absolutely! When it works, like everything else, it's brilliant.

The science...

SE I first started looking at cardiovascular control in notothenioids when it became clear they had a non-adrenergic mediated stress response, which is probably unique among vertebrates. After much arguing with unbelieving reviewers, we showed that this was due to impaired release and downregulated synthesis of catechol-amines. The cardiovascular system is dominated mainly by cholinergic control, along with serotonergic vasoconstriction in branchial vessels. We've utilised pharmacological blockade, bilateral cardiac vagotomy, and heart rate loggers to examine the plasticity of vagal control in the lab and also in free ranging animals. Using the natural myoglobin 'knockout' seen in icefish we characterised how oxygen transfer was accommodated without facilitated diffusion (cardiomegaly, low resistance circulation, huge mitochondrial volume density). Recently we've been tackling cardiorespiratory coupling, and whether it is possible to detect the equivalent of sinus arrythmia when heart rate and ventilation frequency are similar.

Eccentric exercise provides new insight into sensorimotor control of muscle

Uwe Proske answers some questions about a form of exercise that leaves us stiff and sore next day, and how a study of such exercise can be used to better understand muscle and its neural control

Uwe Proske

In recent years there has been an upsurge of interest in the physiology of exercise. One reason for this is that exercise has become a part of most people's lives as we try to maintain our fitness in the face of largely sedentary lifestyles. Then there is the rise in spectator sports, such as football, where we participate by yelling at the TV screen. With it comes a never ending search for better performances by the elite athletes shown on our screens, who are paid astronomic salaries, and whose only concern is how best to avoid exercise-induced injury. That, in turn, raises interest in the physiology of exercise.

Changes in muscle mechanical properties after eccentric exercise

In a simple classification we might identify three different kinds of exercise. The first is concentric exercise, where the contracting muscle shortens, as occurs during most movements. In isometric exercise, muscle length does not change; for example, contracting our arm muscles while grasping a support to hold ourselves upright. Finally, in eccentric exercise, where the contracting muscle lengthens, we use our muscles to control a movement, such as closing a door, without banging it, in the face of a stiff breeze. Other examples of eccentric biased activities include horse riding, downhill walking and kicking a ball. The curious thing about eccentric exercise is that it is the only form of exercise that leaves us stiff and sore the next day. Intense concentric or isometric exercise may reach the point of being painful, but there are no after-effects a day later.

Eccentric exercise, in someone unaccustomed to it, leads to muscle damage. That, in turn, triggers an inflammatory response and the products of the inflammation are thought to sensitise muscle nociceptors, hence the pain. The primary event in the damage process is believed to be disruption of sarcomeres in the exercised muscle fibres (Morgan, 1990; Proske & Morgan, 2001). As the disruption spreads, membranes become torn leading to the uncontrolled release of calcium into the sarcoplasm. The calcium triggers a contracture in parts of the fibre. The contracture persists for several hours, presumably for as long as energy stores allow. The presence of injury contractures in damaged muscle fibres produces a rise in whole muscle passive tension (Fig. 1), which is what we experience as a sensation of stiffness.

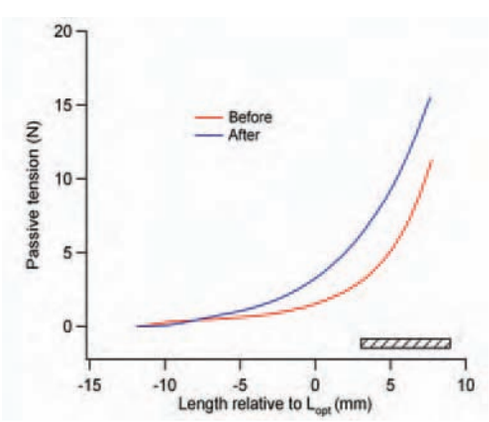


Figure 1. Rise in passive tension after eccentric contractions. Passive tension, in Newtons (N), in the gastrocnemius muscle of the anaesthetised cat, measured during a slow stretch of the muscle (1mm s^{-1}) over the range, L_{opt} –10mm to L_{opt} +8mm, where L_{opt} was the optimum length for active-tension. Red trace, tension before a series of eccentric contractions, blue trace, immediately afterwards. The 50 eccentric contractions were carried out over the length range of L_{opt} +2mm to L_{opt} +9mm (hatched bar). They consisted of active stretches at 50mm s^{-1} during stimulation of the muscle at 80 pulses s^{-1}. After the eccentric contractions passive tension had increased at most lengths, peaking at L_{opt} +3mm. Redrawn from Whitehead *et al* (2003).

It is possible to collapse most of the extra, injury-related, passive tension by subjecting the muscle to a large passive stretch (Whitehead et al. 2003). We are not sure why. One possibility is that the stretch breaks up the region of injury contracture into smaller segments separated by parts of the fibre devoid of contractile material (Whitehead et al. 2003). It occurred to us that one possible role of the warm-up stretches routinely used by athletes before exercise is to keep passive tension levels low and so help maintain a larger range of motion about the joint (Reisman et al. 2005).

The damage to membranes impairs function of the excitation-contraction coupling system. T-tubules may shear off. A consequence for the muscle is a change in the force-frequency relation, and higher rates of stimulation are now required to achieve peak tension (Fig. 2).

Another immediate consequence of muscle damage from eccentric exercise is a shift of the muscle's optimum length for peak active tension, in the direction of longer muscle lengths (Fig. 3). That is, the muscle has to be stretched out further before peak tension levels are reached. The reason is that the disrupted sarcomeres are scattered at random along muscle fibres and typically lie adjacent to still functioning parts of the fibre. This means that, when the functioning sarcomeres develop force and shorten,

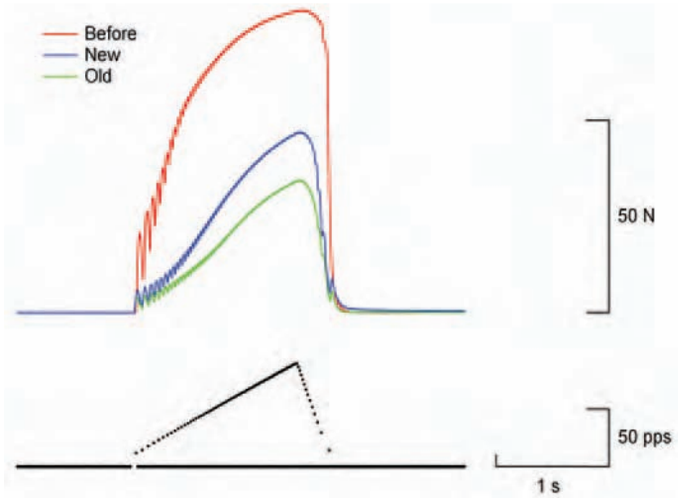


Figure 2. Low frequency fatigue after eccentric contractions. The response of the gastrocnemius muscle of the anaesthetised cat to stimulation at linearly increasing frequency between 0 and 100 pulses s^{-1} over 1.5s followed by a more rapid fall in rate. Stimulus rate (black trace) is shown as an instantaneous frequency display. The red trace is the response of the muscle, measured at the optimum length, before the eccentric contractions. Then the muscle was subjected to 50 eccentric contractions during stimulation at 80 pulses s^{-1} and a stretch of 6mm at 50mm s^{-1}, distributed symmetrically about the optimum length. The green trace is the response to frequency ramp stimulation after the eccentric contractions measured at the original, pre-exercise optimum length. The blue trace is the response measured at the new post-exercise optimum. Note that before the eccentric contractions the twitch was 27% of the tetanic tension, afterwards 10% (old optimum) and 13% (new optimum). Redrawn from Parikh *et al.* (2004).

they not only have to raise tension in the tendon, but in the adjacent non-functioning sarcomeres as well. The extra compliance represented by disrupted sarcomeres leads to a shift in the length-tension curve of the muscle in the direction of longer lengths. The shifted curve is also a little narrower, as it represents activity of a smaller number of sarcomeres in series.

It is a common misconception that muscle damage from eccentric exercise is the result of the high level of tension generated during the active stretches. It is true that during the stretch force rises above isometric levels, but it is a relatively simple matter to show that high force levels, as such, are not responsible for the damage. We have done this in two ways (Morgan *et al.* 2004).

First, in an animal preparation we compared the amount of muscle damage from 50 eccentric contractions in fresh unfatigued muscle with previously fatigued muscle, by determining the fall in peak active tension and the shift in optimum length.

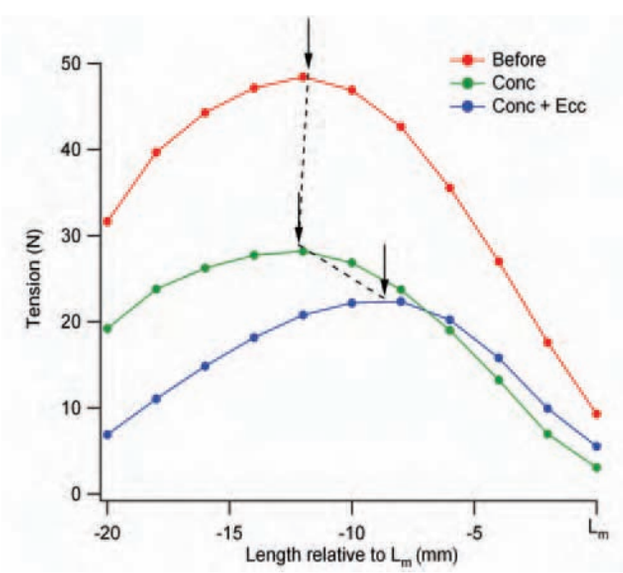


Figure 3. Shift in length-tension curve after eccentric, but not concentric contractions. The tension of gastrocnemius of the anaesthetised cat was measured at different muscle lengths over the full physiological range up to maximum (Lm) using 250ms tetani at 80 pulses s^{-1} . The red trace represents the length-tension curve measured at the start of the experiment. The muscle was then subjected to 200 concentric contractions where the muscle actively shortened by 12mm at 60mm s^{-1} symmetrically about the optimum length. The green curve shows the post-concentric length-tension relation. Peak tension had fallen by 42% and optimum length (arrows) had slightly shortened (0.3mm, dotted line). The muscle was then subjected to a further 10 eccentric contractions, arranged to lie entirely on the descending limb of the length-tension relation. The blue trace shows the length-tension relation after the eccentric contractions. Peak tension had fallen by a further 12% and optimum length had shifted by 3.2mm in the direction of longer lengths (dashed line and arrows). Redrawn from Morgan *et al.* (2004).

We fatigued one muscle portion, reducing its tension by 40%, by means of a series of concentric contractions. It is known that concentric contractions are not accompanied by muscle damage. Consistent with that view was the finding that the concentric contractions were not accompanied by a shift in optimum (Fig. 3). The eccentric contractions were given to both preparations, the fatigued muscle and the fresh, unstimulated muscle. Both showed a subsequent fall in force. The size of the fall was less in the previously stimulated muscle, since many of its muscle fibres were already fatigued. More importantly, both preparations showed a similar shift in optimum length, suggestive of similar amounts of damage (Morgan *et al.* 2004). That raises the more general point that a drop in force, as such, is not a good indicator of how much damage has been produced, because of the additional effects of fatigue. The shift in optimum is more reliable.

In another experiment we divided the muscle nerve supply into different sized portions, in terms of the tension they generated during stimulation. Eccentric contractions of each portion led to a shift in optimum length and a fall in force. The sizes of the shifts and the relative force drops were not correlated with the amount of force generated by each piece of muscle before the eccentric contractions.

Our conclusion is that force levels are not a major determinant of the amount of damage from eccentric contractions. The factor we consider the most

important is the length range over which the active stretches are carried out. If the stretch includes a portion of the descending limb of the length-tension curve, the region of sarcomere instability (Morgan, 1990), damage is more likely.

Implications for proprioception

It is a common experience after a period of intense exercise to feel unsteady on the feet and have difficulty in carrying out skilled movements. Think of the marathon runner staggering off the track at the end of the course. This is not just a matter of muscle weakness from fatigue; there is evidence that there is a disturbance to the sense of tension and the sense of limb position after a period of eccentric exercise (Brockett *et al*. 1997). So the staggering athlete may be unsure of where their feet are if they are not looking at them.

We considered the possibility that eccentric exercise not only damaged muscle fibres but also disturbed the function of muscle sense organs, the muscle spindles and tendon organs. We therefore studied, in an animal model, the response properties of spindles and tendon organs after a severe bout of eccentric exercise (Gregory *et al.* 2002; 2004). It turned out that there was no evidence of disturbance to normal function of muscle receptors. This result meant that we had to reassess the claims about eccentric exercise and proprioception.

We therefore repeated a series of psychophysical experiments on human subjects and showed, specifically, that after a period of eccentric exercise subjects made large errors in an isometric force matching task (Weerakkody *et al.* 2003) and in a limb position matching task (Walsh *et al*. 2004). The size of the errors was correlated with the size of the force drop after the exercise (Fig. 4). This led us to conclude that in determining a given level of force in their muscles, or the position in space of their unsupported limbs, subjects were not just relying on information coming from sense organs in the muscle, but were using as a force or position cue the amount of effort required to carry out the task.

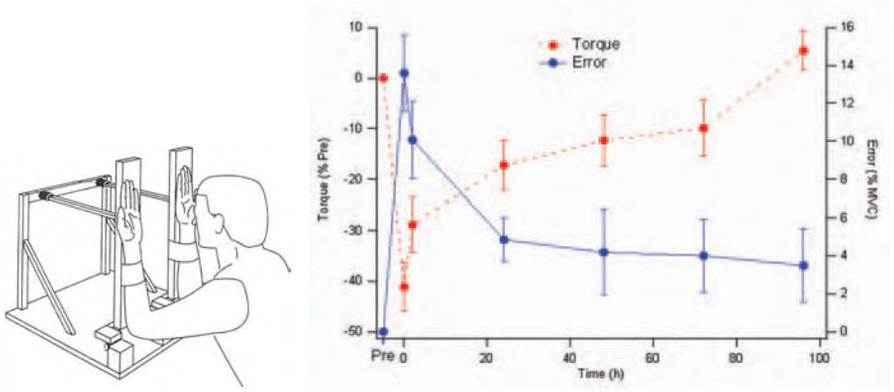


Figure 4. Errors in a force matching task after eccentric exercise. *Left panel*, subjects had their forearms strapped to a pair of lightweight paddles which were fixed in a vertical position by metal struts at the ends of which were strain gauges. The subject could see the force output of one arm on a computer screen, which they were instructed to match with their other arm, without visual feedback. *Right panel*, after a series of eccentric contractions of elbow flexor muscles torque fell by 40% and then gradually recovered over the next four days (red dashed trace). Force matching errors (blue trace) mirrored the fall in torque. Errors were expressed as percent control MVC (maximum voluntary contraction), which was assigned a value of zero. Similarly, control torque was given as zero. Redrawn, in part, from Weerakkody *et al.* (2003).

It is believed that the sense of effort or of heaviness is generated within the brain and, as such, is independent of feedback from the body periphery. A way to think of it is to imagine that, every time we carry out a contraction, a copy of the motor command to the muscles is sent back to sensory areas in the brain to generate a sense of effort.

During intense exercise of all kinds the muscle will fatigue, and now more effort will be required to generate a given level of muscle force. That, in turn, leads to a disturbance of the sense of force and the sense of limb position, hence the staggering marathon runner.

Concluding comments

Eccentric exercise has turned out to be an interesting topic of study. It has taught us something about the damage process in muscle following such exercise and it has led us to reassess current views about limb proprioception. There is the promise of more in the future. How is the soreness from exercise generated? Can it be minimised by training? Are muscle strains related to the damage from eccentric exercise? How can they be avoided? It is an old observation that, when one question leads to many others, we know that we are breaking important new ground.

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Myofilament lattice plasticity in airway smooth muscle

Our mechanical, energetic, and structural studies suggest that airway smooth muscles adapt to longer lengths by placing more contractile elements in series, that this filament-lattice plasticity is facilitated by thick-filament evanescence, which dissolves partially during relaxation, and that filament reformation is sufficiently rapid to account for the observed velocity slowing and some of the force rise during the onset of activation

Lincoln Ford

Some years ago, while Chun Seow and I were studying tension transients in skinned skeletal muscle, he asked how he might use our mechanical techniques to study smooth muscle. He had done his doctoral work on airway smooth muscle in Winnipeg and planned to return both to Canada and to smooth muscle after working with me. My response was that filament lattice plasticity facilitated by myosin filament evanescence might be a fruitful area.

The discovery of sliding filaments in skeletal muscle led to early searches for similar filaments in smooth muscle. Thin filaments were always seen, but thick-filament descriptions varied with respect to both shape and filament density. Some early workers (Kelly & Rice, 1968; Shoenberg, 1969) proposed that this variability resulted from thick filaments being evanescent, dissociating partially during relaxation and reforming upon activation. Attention turned elsewhere, however, and this issue disappeared nearly completely from the literature.

But the suggestion of thick filament evanescence was appealing. Muscle length changes in the walls of some hollow viscera are so large that they are unlikely to be accommodated by a fixed array of filaments, and filament evanescence could facilitate plastic adaptations to greater length ranges. Our first experiments confirmed that smooth muscle adapts to longer lengths by placing more contractile elements in series; developed force was nearly constant over a 3-fold range of length while velocity and compliance approximately doubled (Pratusevich *et al*. 1995). The constant force is predicted by the addition of new filaments in series allowing the thick and thin filaments to remain near their optimum overlap. The velocity and compliance increases are expected from the addition of new contractile elements in series.

Another prediction of the model derives from the consideration that thick filaments lengthen as they form. Since the crossbridges on each separate filament are arrayed in parallel, force should increase in proportion to filament lengthening. But fewer of the longer filaments are required to span the length of the muscle, so that there will be fewer of the longer filaments arranged in series. If the velocity of the individual crossbridges and filaments is independent of filament length, the overall muscle velocity will be proportional to the number of filaments in series. A second study confirmed that velocity declined during the rise in activation, and when correction was made for changes in the level of activation, the velocity decline was exactly balanced by a rise in force (Seow *et al*. 2000). This finding raised the question of whether filament formation is sufficiently rapid to account for the mechanical findings.

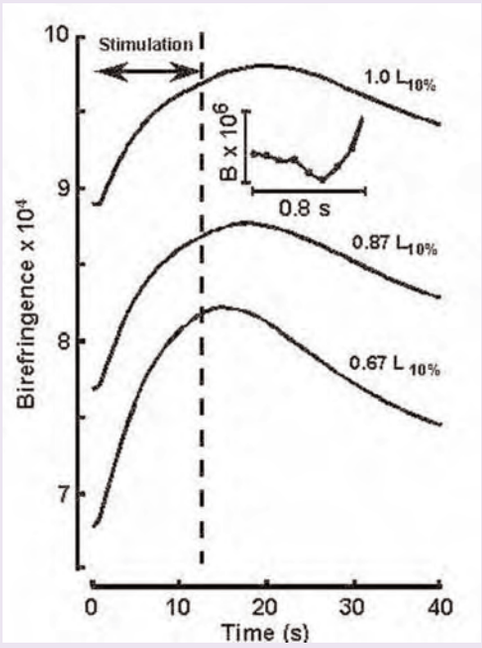

Figure 1. Absolute values of birefringence measured continuously during tetanic stimulation of pig trachealis muscle at three different lengths during 12.5 s tetani. L10% is the reference length at which rest tension is 10% of developed force. The other two lengths were 87% and 67% of this length. Interrupted vertical line indicates the time when stimulation ended. Note that birefringence rises during the period of stimulation and continues to increase for a short time after stimulation ends. In skeletal muscle, the birefringence signal declines during activation and this change is believed to be due to movement of the crossbridge heads away from the thick filament backbone. This consideration suggests that there may be two components to the birefringence signals here. One is an increase due to thick filament formation. The second is a decrease due to movement of crossbridges away from the thick filament backbone. The rise at the end of stimulation, and possibly the slight fall before the intial rise shown in the inset under the upper record, are likely due to this crossbridge movement. From Smolensky *et al.* (2005).

After returning to Canada, Chun Seow completed several quantitative electron microscope assessments of thick filament density made in steady states, confirming that thick filament mass is increased during contractures (Herrera *et al*. 2002) and at longer lengths (Kuo *et al*. 2003). Earlier quantitative studies on rat *anococcygeus* muscle (Godfraind-De Becker & Gillis, 1988; Gillis *et al*. 1988) also concluded that thick filament density increased during contractures when measured both by electron microscopy and by optical birefringence. Birefringence is a well-known property of striated muscle because the A-bands are defined by being anisotropic, i.e. birefringent, and it is now known that the birefringence is due to the myosin filaments. Thus, the strength of birefringence would be expected to reflect myosin filament density. Godfraind-De Becker and Gillis' pioneering birefringence measurements had low time resolution, but their results suggested that this optical signal, if measured more rapidly, could be used to track filament formation if it occurs. Accordingly, we built the necessary apparatus to track birefringence electronically and extended the earlier findings to show that:

• birefringence was increased at longer lengths, as predicted by our mechanical experiments (Smolensky *et al*. 2005; Fig. 1);

• it increased during stimulation with about the same time course as force, confirming that filament formation is rapid enough to account for the velocity slowing.

All of our work has been done on the *trachealis* muscle of medium-sized mammals (dog, sheep, and pig), because Chun had done his doctoral work on this preparation. It was a fortunate choice; *trachealis* is composed of straight bundles of parallel cells with little connective tissue and is therefore ideal for mechanical studies, unlike many other smooth muscles, which have crisscrossed arrays of muscle bundles and much more connective tissue. The preparation is emphasized to point out that the filament evanescence and long length range of our preparation may not be detected easily in smooth muscles where large length changes are prevented by a heavy investment of connective tissue, or in muscles that do not normally relax fully when left unstimulated. Godfraind-De Becker & Gillis (1988), for example, failed to find the same increase in birefringence of *taenia coli* that they did in rat *anococcygeus,* and noted that the *taenia coli* showed spontaneous activation. Similarly, Herlihy & Murphy (1973) found a much shorter length range in arterial smooth muscle, which is heavily invested with elastic tissue.

Acknowledgements

Our work has been supported by USPHS Grant # RO1-HL52760. We thank Sir Andrew Huxley for many helpful suggestions and for his efforts to educate us in the mechanisms of birefringence.

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Oxygen and the ocular lens

A key to understanding nuclear cataract?

Richard McNulty (left) and Steven Bassnett

The ocular lens is located behind the iris and in front of the gel-like vitreous humour. Normally the lens cannot be seen, and with good reason: its function is to transmit and focus light. Any disturbance in lens metabolism is likely to result in opacification of the tissue, a condition known as cataract. Although eating a diet rich in anti-oxidants and vitamins may slightly decrease one's chances of getting a cataract, the only successful treatment currently available is surgical removal of the cataractous lens.

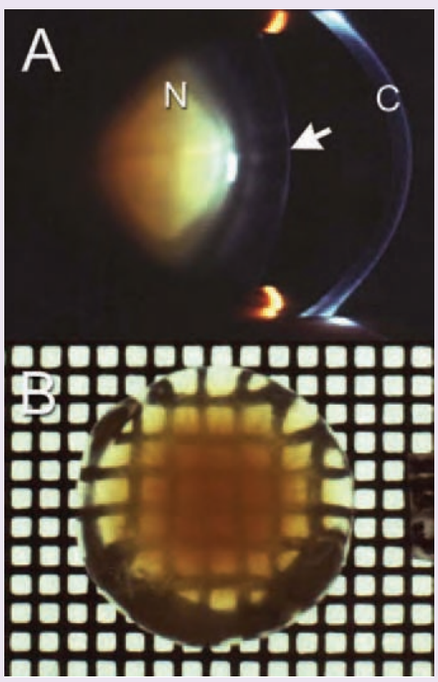

Figure 1. Photograph of a nuclear cataract. (A) The cataractous lens can be visualized in vivo using a slit lamp camera. The lens nucleus (N) has become opaque while the superficial lens tissue remains transparent. The location of the lens surface is indicated by an arrow. The cornea (C) is also visible. (B). The cataractous lens was removed surgically and photographed against a grid. Note how the opaque nucleus blocks light transmission though the centre of the lens. Images adapted (with permission) from Marcantonio *et al*. (1980).

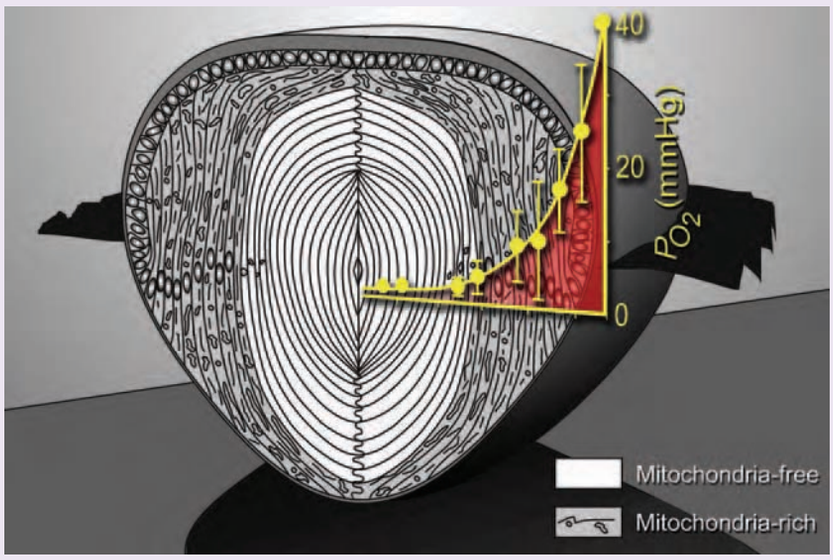

Figure 2. Cellular architecture of the lens. The lens has a laminar structure. The superficial cell layers contain mitochondria while the central, oldest cells do not. Oxygen utilization by mitochondria in the surface layers generates a steep gradient of dissolved oxygen and results in a condition of permanent hypoxia in the innermost cells.

The most common type of cataract is age-related nuclear cataract (ARNC), a yellowy-brown cataract located in the lens centre (Fig. 1). This type of cataract is probably the single leading cause of global blindness. The concept that molecular oxygen may play a key role in the development of ARNC has emerged from two types of study. Firstly, detailed biochemical analyses of ARNC cataracts have revealed widespread oxidation of lens proteins. Secondly, oxygen has been implicated directly in the cataracts that form as an unwanted side effect of certain clinical procedures. For example, nuclear cataracts often appear in patients following hyperbaric oxygen (HBO) therapy or vitrectomy surgery (Palmquist *et al*. 1984; Holekamp *et al*. 2005). HBO appears to overwhelm the lens with oxygen, causing oxidative stress. During vitrectomy, a surgical treatment for retinal disease, the vitreous gel inside the eye is removed and replaced with a physiological salt solution. Convective mixing of this solution within the eye may lead to the delivery of oxygen from the highly vascular retina to the lens. Because HBO- and vitrectomy-associated cataracts closely resemble ARNC clinically and biochemically, it has been postulated that oxygen may also have a causative role in the latter.

The lens is normally shielded from the potentially damaging effects of oxygen by virtue of both its location and unusual physiology. The interior of the eye is a relatively hypoxic environment, containing levels of oxygen only 10% of that found in arterial blood. The lens lacks a blood supply (hemoglobin would absorb light) and oxygen destined for the inner cells must, therefore, diffuse through the superficial tissue layers. Recently, we proposed a new model of the lens in which metabolic processes in these outer cell layers generate standing gradients of oxygen within the tissue. As a result, cells of the lens core exist in a permanently hypoxic state (Fig. 2).

Only the outermost, and youngest, lens cells have a full complement of organelles. Respirometric measurements have indicated that mitochondria located in these cells consume 90% of the oxygen entering the lens and, by so doing, reduce the concentration of dissolved oxygen in the lens core to <2 μM (McNulty *et al.* 2004). In these permanently hypoxic cells the introduction of oxygen is likely to have profound and deleterious effects. Interestingly, the lens meets most of its energy needs not from oxidative phosphorylation but from glycolysis. Indeed, various indices of lens viability (including tissue clarity) are preserved in the complete absence of oxygen. Perhaps uniquely in this tissue, therefore, the role of mitochondria in generating ATP via oxidative phosphorylation might be secondary to their role in excluding oxygen from the lens centre.

Because lens core hypoxia appears to depend critically on mitochondrial function, manipulations that interfere with mitochondrial metabolism result in the rapid flooding of the core with oxygen. For example, simply lowering the temperature from 37ºC to room temperature is sufficient to cause a rapid rise in oxygen concentration in the lens core. This may be a clinically pertinent observation because chilled solutions are often infused into the eye during ocular surgery. As noted above, nuclear cataract is an unfortunate side effect of many such surgeries and may result, at least in part, from the exposure of the lens core to oxygen during the procedure. With aging, mitochondrial function in general is known to decline. It remains to be determined whether reduced mitochondrial oxygen consumption in the outer cell layers of the aging lens compromises core hypoxia and thus triggers nuclear opacification.

Acknowledgement

These studies were supported by NIH grants R01-EY015507 (to SB), EY02687 (Core Grant for Vision Research) and an unrestricted grant to the Department of Ophthalmology and Visual Sciences from Research to Prevent Blindness. SB is an RPB William and Mary Greve Scholar.

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New insights into secretion in epithelial cells

Peter Thorn

Pancreatic acinar cells have long been used as a model system to study the mechanisms that underlie polarized secretion. The determination of the pathways of synthesis of digestive enzymes (the major secretory product) in the endoplasmic reticulum, and then their passage through the Golgi and condensing vacuoles into the secretory granules, was the basis for the Nobel Prize in Physiology given, as part of a joint award, to GE Palade in 1974. Palade's work showed that the final stage of secretion, the release of secretory products to the outside, depends on the fusion of secretory granule membrane with the apical plasma membrane. The year before this Nobel award, it was demonstrated that the trigger for this digestive enzyme release was a rise in calcium (Matthews *et al*. 1973).

Modern imaging techniques now make it possible to observe these final steps of granule fusion with the plasma membrane, the process of exocytosis. Perhaps the most interesting findings indicate that secretion in these cells may follow processes somewhat distinct from those found in neurones and endothelial cells. Firstly, it appears as if almost all aspects of exocytosis are slow. Secondly, there is evidence that granule membrane retrieval, endocytosis, may follow a distinct pathway.

Looking at the temporal aspects of exocytosis, the exocytotic response in acinar cells follows a calcium rise with a delay of seconds (Ito *et al.* 1997) compared with millisecond delays seen in neurones. After fusion of the granule and apical plasma membrane, granule contents are lost relatively rapidly (~10 s, Thorn & Parker, 2005) but the granule stays at the plasma membrane (Nemoto *et al.* 2001), with direct evidence that the fusion pore stays open for many minutes (Thorn *et al.* 2004).

Looking at endocytosis, in principle, the granule membrane could collapse into the plasma membrane and then be retrieved or it could be that the whole granule is recaptured. In the latter case we are left with a basic problem – how could it be refilled with its proteinaceous contents? Recent experiments suggest a third possibility. We have shown that the fusion pore apparatus forms a barrier to the movement of lipids even as the granule disappears, a time when we presume endocytosis is taking place. This has led to our proposal that granule membrane recovery (endocytosis) may proceed in a piecemeal fashion (Fig.1) with small pieces of membrane gradually recovered from the original granule and then reconstituted in the Golgi into a new granule ready for another round of exocytosis (Thorn *et al*. 2004). For a cell, this method of endocytosis would provide an efficient mechanism of recycling intact granule membrane without the need to re-sort the membrane constituents.

Recycling of granule components is supported by early experiments showing that the lifetime of granule membrane proteins is much longer than the lifetime of the proteins that make up the granule contents (Jamieson & Palade, 1971). In addition, the model of piecemeal endocytosis is specifically supported by freeze-fracture experiments in salivary gland acinar cells, where differences in intramembrane particle density between the apical plasma membrane (high density) and the granule membrane (low density) are maintained even after exocytosis and apparently during endocytosis (De Camilli *et al.* 1976).

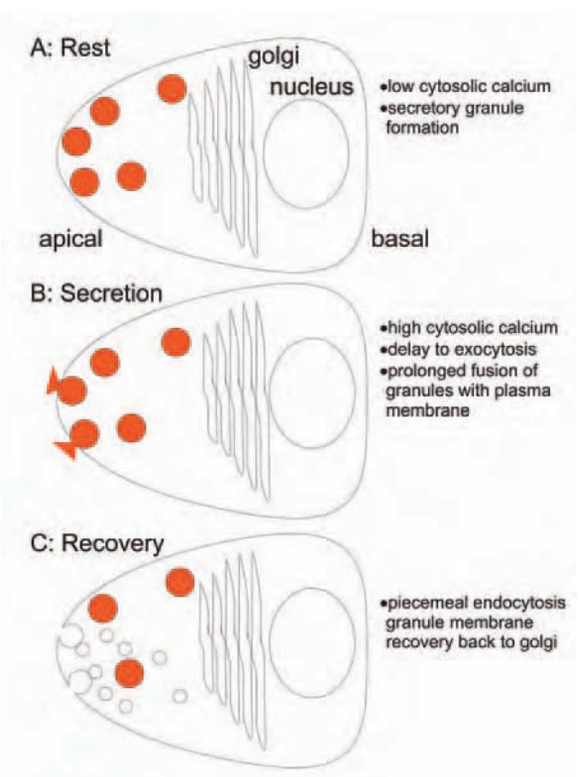

Figure 1. A schematic outline of secretion in pancreatic acinar cells. A: At rest secretory granules formed at the golgi are transported to the apical region; B: A rise in cytosolic calcium triggers exocytosis after a delay of seconds; once fused with the plasma membrane granule contents are lost within 10 seconds but granules linger with an open fusion pore, for many minutes; C: Membrane recovery, endocytosis, may follow a route of piecemeal recapture from the secretory granule and recycling at the golgi apparatus.

However, unfortunately there is no corresponding data for pancreatic acinar cells since the intramembrane particle densities, prior to exocytosis, are the same in the plasma membrane and granule membrane. Further, recent evidence apparently contradicts the idea that the fusion pore blocks interchange between the granule and the plasma membrane and suggests that syntaxin 2, a plasma membrane protein thought to be important in exocytosis, may get into the granule membrane after exocytosis (Pickett *et al.* 2005). Clearly, more work is needed to understand the endocytotic process in epithelial cells.

The specific proteins that might regulate the slow kinetics of epithelial cell exocytosis and regulate the process of endocytosis are not known. Proteins known to control exocytosis in other cells, have been identified on the apical plasma membrane and on the secretory granule, but the specific proteins involved have yet to be identified; even the calcium sensor itself remains unknown. Imaging the processes of exocytosis and endocytosis in epithelial cells and defining the proteins involved will certainly be an exciting challenge for the future.

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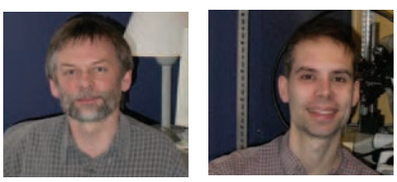
The emerging role of calcium-dependent exocytosis in ATP release from nonexcitable cells

The recent demonstration that intracellular calcium elevation is a sufficient trigger for ATP secretion from epithelial cells and fibroblasts strongly supports the involvement of exocytosis



Ryszard Grygorczyk (left) and Francis Boudreault

The role of ATP as an extracellular signalling molecule is now widely accepted in a broad spectrum of biological systems. The entire field of purinergic signalling is expanding rapidly, as exemplified by the recent launching of a journal entitled *Purinergic Signalling* (Burnstock, 2004). This progress has been driven by the cloning of several members of the large family of nucleotide-activated cell surface receptors and of the ubiquitously distributed classes of ectoenzymes that catalyze nucleotide breakdown and interconversion (Lazarowski *et al.* 2003). Recent years have also been marked by growing interest in the mechanisms of nucleotide release, especially from epithelial and other nonexcitable cells, where these mechanisms remain incompletely understood. Because cellular ATP release can be evoked by various stimuli, including mechanical perturbation, cell swelling, hypoxia and a number of agonists via receptor-mediated stimulation, several release mechanisms may be involved. In addition, basal release from unstimulated cells is well-documented and has important physiological implications for the tonic autocrine activation of purinergic signalling pathways.

It is generally accepted that regulated exocytosis is responsible for ATP release from neuronal and secretory cells, in which specialised granules containing ATP, together with other extracellular mediators, have been identified. Such dedicated granules have not been explicitly found in most epithelial cells, and alternative mechanisms of ATP secretion, such as ATP-conducting channels, have been sought. While there is strong evidence against the involvement of the cystic fibrosis transmembrane conductance regulator (CFTR) chloride channel, mechano-sensitive or volume-sensitive chloride channels (VSCC), ATP permeability has been convincingly demonstrated for voltage-dependent anion channels (VDAC) and connexin hemichannels. VDAC-like channels have been detected by the patch clamp technique in the plasma membrane of numerous cells, but not always confirmed by immunocytochemical techniques. Because patch clamping inevitably imposes major stresses on cells, the physiological significance of these channels on the cell surface should be viewed with caution. The role of connexins may be limited to specific cells or experimental conditions, e.g. un-physiologically low extracellular Ca^{2+}, and numerous preparations have provided no evidence of their involvement in ATP release (Guyot & Hanrahan, 2002; Lazarowski *et al*. 2003).

Alternatively, ATP can be released by regulated exocytosis, a Ca^{2+}-dependent process that engages ATP-loaded granules and requires SNARE proteins for membrane fusion. Are these elements present in epithelial cells? In *The Journal of Physiology*, we (Boudreault & Grygorczyk, 2004) recently provided evidence of a tight correlation between ATP release induced by hypotonic cell swelling and elevation of intracellular Ca^{2+} ($[Ca^{2+}]_i$). Hypotonicity-evoked ATP release coincided with the peak of $[Ca^{2+}]_i$ elevation in the three cell types studied: human lung alveolar A549 cells (Figure 1*a*), human airway epithelial cells 16HBE14o$^-$ and 3T3 fibroblasts. ATP release was almost completely

abolished by BAPTA chelation of $[Ca^{2+}]_i$, while Ca^{2+}-ionophore induced ATP release in the absence of hypotonic shock (Figure 1 *b*, *c*). Thus, Ca^{2+} is a necessary and sufficient signal for ATP release, although the magnitude of release can be modulated by other factors. Both hypotonicity-induced ATP release and $[Ca^{2+}]_i$ elevations in A549 cells were completely abolished at 10°C, suggesting that exocytotic release is involved and is a dominating mechanism in these cells. Because most ATP was secreted from swollen cells prior to the regulatory volume decrease, a contribution of conductive release via VSCC or exocytotic insertion of other ATP-conducting anion channels could also be excluded with confidence.

Specialised ATP-filled granules have not been definitively identified in non-excitable cells, but other vesicles may contribute to exocytotic ATP release. Due to its fundamental role as an energy source and in protein phosphorylations some ATP is expected in the lumens of most, if not all, cell organelles, including the endoplasmic reticulum (ER), Golgi, endosomes, lysosomes and various membrane-trafficking vesicles. Indeed, ATP was found in the ER lumen and in secretory vesicles from large numbers of non-neuronal cells, and protein transport vesicles were recently shown to contribute to ATP release from oocytes (Maroto & Hamill, 2001). Thus, vesicles of different origins could contribute to ATP secretion, and their relative contributions will require experimental verification.

Further supporting evidence for exocytosis includes the presence of SNARE proteins, key mediators of intracellular membrane fusion events in all eukaryotic cells. Disruption of SNARE complexes by *C botulinum* toxins abolished ATP release from intestine 407 cells (Van der Wijk *et al.* 2003). In neuronal and endocrine cells, SNARE complex assembly during exocytosis is tightly coupled to Ca^{2+}, but less is known about these mechanisms in epithelia. Because different SNARE proteins are generally localized to specific organelles and are involved in only specific trafficking

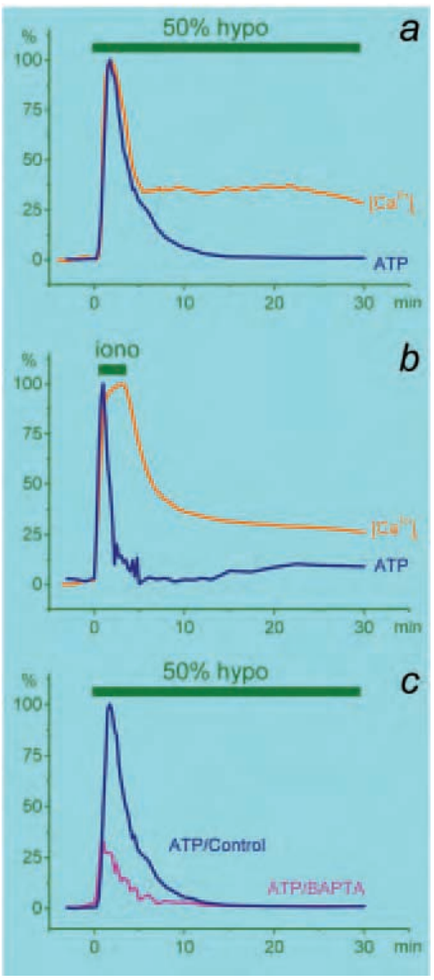


Figure 1. ATP release from A549 cells requires $[Ca^{2+}]_i$ elevation.
A, Effect of acute 50% hypotonic shock on the rate of ATP release (blue trace) and $[Ca^{2+}]_i$ changes (orange trace) in confluent A549 cell monolayers. Note a tight correlation between the peak of ATP release and the peak of $[Ca^{2+}]_i$. Ionomycin induces ATP release in the absence of hypotonic shock, *B*, while hypotonic shock-evoked ATP release is inhibited by chelating $[Ca^{2+}]_i$ with BAPTA, *C*. The graphs show relative changes (in %) of the rate of ATP release and of $[Ca^{2+}]_i$, normalized to their peak values. Redrawn from Boudreault & Grygorczyk (2004).

pathways, one could speculate that different vesicular pools may contribute to different modes of ATP release, depending on the stimuli. In this context, it is interesting that lysosomes are reported to behave as Ca^{2+}-regulated exocytotic vesicles in fibroblasts and epithelial cells (Rodriguez *et al*. 1997).

Further studies are required to determine the prevalence and physiological significance of different ATP release mechanisms. While channel-mediated release may be important in some cell types, the recent demonstration that increased $[Ca^{2+}]_i$ is a sufficient trigger for ATP secretion from epithelial cells and fibroblasts strongly supports the involvement of exocytosis. Because diverse stimuli could elevate $[Ca^{2+}]_i$, ATP release via regulated exocytosis has the potential to be a widespread mechanism operating in many cell types.

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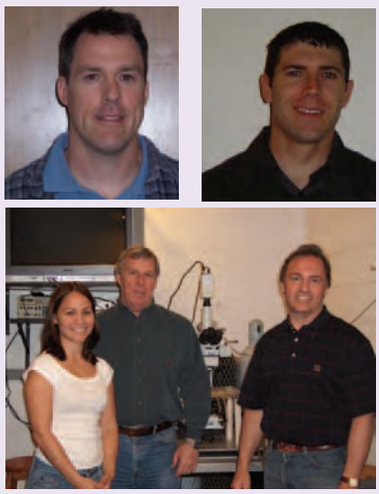
Control of oxygen delivery within skeletal muscle

The delivery of O_2 to contracting myocytes ultimately limits the scope of oxidative metabolism and is also an important determinant of substrate selection. New data provide insight into the matching of O_2 supply and demand in muscles of differing fibre type



Paul McDonough (top left), Brad Behnke (top right), Danielle Padilla (left), Timothy Musch and David Poole (above)

Sustained muscular activity requires a continuous and adequate O_2 supply during which blood flow ($\dot{Q}$) may increase more than one order of magnitude. In general, convective O_2 transport ($\dot{Q}O_2$), the product of Q and O_2 concentration, increases in proportion to the elevated metabolic rate ($\dot{V}O_2$) (reviewed by Poole, 1997). However, within the exercising muscles themselves, little is known about the matching of $\dot{Q}O_2$ and $\dot{V}O_2$. This information is crucial to understanding muscle energetics and function during exercise, because the matching of $\dot{Q}O_2$ and $\dot{V}O_2$ determines the pressure of O_2 within the microvasculature ($PmvO_2$) which drives O_2 diffusion from the blood into the myocyte for consumption by the mitochondria (Fig. 1). In addition, $PmvO_2$ helps regulate intracellular PO_2 which determines the cellular energetic status (Wilson *et al*. 1977; Hogan *et al*. 1992; Richardson *et al*. 1995). Across the spectrum of muscular activities which require varying degrees of muscular power, speed or endurance, there is a differential and specific recruitment of muscle fibre types. Muscle fibres have traditionally been differentiated based upon contraction speed and metabolic capacity (i.e. slow-twitch, highly oxidative (Type I), fast-twitch, oxidative/glycolytic (Type IIA), and highly glycolytic (Type IIB/X)). What is not universally appreciated is that these fibre types also have markedly different $\dot{Q}O_2$ responses. Specifically, highly oxidative fibres (Type I and IIA) receive the greatest $\dot{Q}O_2$, while glycolytic fibres receive a relatively parsimonious $\dot{Q}O_2$ (Armstrong & Laughlin, 1983).

Recently, novel phosphorescence quenching techniques have facilitated investigation of the relationship between $\dot{Q}O_2$ and $\dot{V}O_2$ across the spectrum of fibre types (Behnke *et al*. 2003; McDonough *et al*. 2005). At rest and during muscle contractions, slow-twitch soleus muscle regulates its $\dot{Q}O_2/\dot{V}O_2$ ratio at a far higher value than its fast-twitch counterparts (medial and superficial gastrocnemius) (Fig. 2). As a consequence of this behaviour, the soleus muscle sustains a substantially higher $PmvO_2$, thus facilitating high rates of O_2 transport within the fibres of this muscle. Moreover, if that elevated $PmvO_2$ regulates intracellular O_2 levels above those found in fast-twitch muscle (fibres) it will facilitate an improved cellular energy state during contractions (↑ [ATP]/[ADP][Pi], with associated improvements in [PCr]/[Cr] and redox state; Wilson *et al*. 1977; Hogan *et al*. 1992). This effect will be independent of the oxidative or glycolytic capacity *per se* and will mandate faster $\dot{V}O_2$ kinetics at the onset of contractions coupled with a decreased consumption of finite intramuscular glycogen stores and improved contractile function in the fibres of the soleus (Jones & Poole, 2005).

There is compelling evidence that arteriolar vasodilator capacity is lower in fast-twitch muscle via several mechanisms, which include a decreased endothelial nitric oxide synthase activity, decreased sensitivity to endothelial vasodilation and increased sensitivity to noradrenaline (Delp, 1999; Delp *et al*. 2000). This is the most probable cause of the lowered $PmvO_2$ in fast- versus slow-twitch muscles. Mathematically, the reduced $\dot{Q}O_2/\dot{V}O_2$ ratio (i.e. ↓$PmvO_2$) in fast-

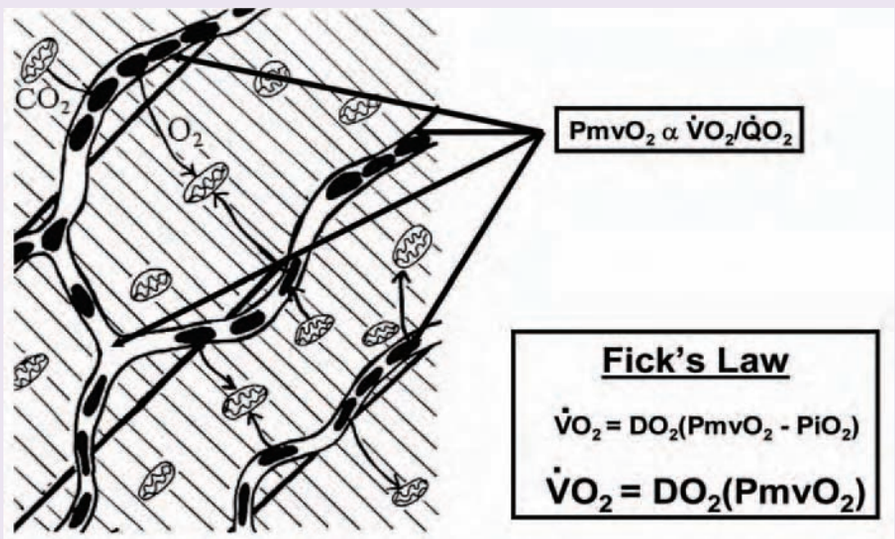


Figure 1. A diagrammatic representation of Fick's law that describes the diffusive flux of O_2 ($\dot{V}O_2$) into the myocyte from the microvasculature. Notice that when intracellular PO_2 (PiO_2) falls to extremely low values during contractions (Richardson *et al.* 1995), $\dot{V}O_2$ can be approximated with little error as the product of muscle O_2 diffusing capacity (DO_2) and microvascular PO_2 ($PmvO_2$). With a higher $PmvO_2$ in slow- compared with fast-twitch muscle fibres, O_2 diffusion into the fibres will be enhanced and there is also the opportunity to raise PiO_2 and thereby increase the intracellular energy state which improves muscle function (see below).

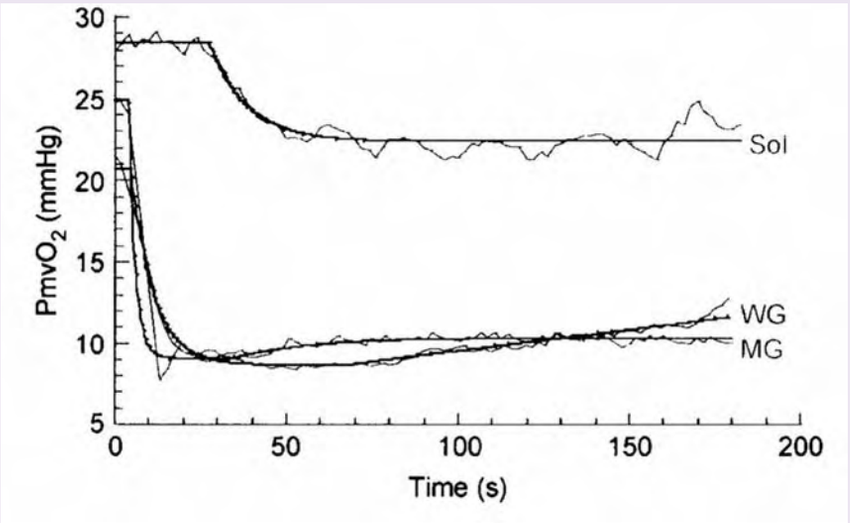


Figure 2. Microvascular O_2 pressure ($PmvO_2$) profiles for soleus (Sol), medial gastrocnemius (MG) and white gastrocnemius (WG) in response to 1 Hz contractions. Time 0 denotes the onset of contractions. Note the substantially higher $PmvO_2$ in Sol (compared to MG or WG) that facilitates greater diffusional O_2 transport into the fibres. In the absence of differences in oxygen delivery ($\dot{Q}O_2$) this would translate into a greater $\dot{V}O_2$ in MG and WG. However, the markedly blunted $\dot{Q}O_2$ response in these two fast-twitch muscles actually results in a much lower $\dot{V}O_2$ and forces them to rely more on fractional O_2 extraction than their slow-twitch counterparts (McDonough *et al*. 2005).

twitch muscle could arise from an elevated $\dot{V}O_2$. However, this is not the case as $\dot{V}O_2$ is lower both at rest and during contractions in fast *versus* slow-twitch muscle (Behnke *et al*. 2003; McDonough *et al*. 2005).

Conclusions

There is a differential $\dot{Q}O_2$-$\dot{V}O_2$ matching and thus $PmvO_2$ in slow- and fast-twitch muscle that is responsible, in part, for their metabolically diverse response to contractions (i.e. oxidative *versus* glycolytic energy production, substrate selection, $\dot{V}O_2$ kinetics and maximal $\dot{V}O_2$). This might constitute one mechanism by which ageing and diseases such as heart failure and diabetes (which may alter the muscle fibre type and/or impair endothelial function) will reduce $PmvO_2$, thereby impairing diffusive blood-myocyte O_2 transport and placing a low limit on exercise tolerance. Therapeutic interventions need to be developed that target preservation or restoration of arteriolar endothelial function. This strategy would elevate $PmvO_2$ at rest and during exercise and improve mobility and health outcomes in these diseases.

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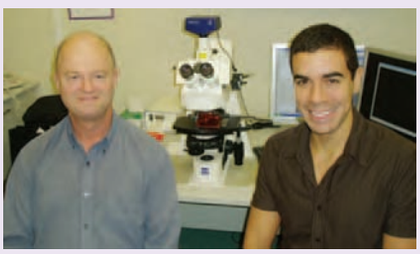
How do receptor-associated proteins regulate the turnover of receptors at a synapse?



William Phillips (left) and Othon Gervásio

The packing of acetylcholine receptors (AChRs) into a post-synaptic AChR cluster ensures efficient synaptic transmission at the neuromuscular synapse. The AChR cluster is formed during embryonic development in response to signalling pathways initiated when neural agrin (released from the motor nerve) activates the **Mu**scle **S**pecific **K**inase, MuSK (Sanes & Lichtman, 2001). A protein called rapsyn that binds the cytoplasmic domains of the AChR is then thought to cross-link AChRs and attach them to the cytoskeleton (Fig. 1). While rapsyn is essential for forming AChR clusters, it is not clear how MuSK activation initiates rapsyn-mediated AChR clustering (Sanes & Lichtman, 2001).

Humans with subtle mutations in the rapsyn coding sequence are born with AChR clusters but their post-synaptic AChR density is impaired (Ohno *et al.* 2002). How then does wild-type rapsyn contribute to the postnatal maturation of healthy synapses?

Life-cycle of a receptor

We tagged rapsyn with jellyfish green fluorescent protein and introduced the chimeric protein (rapsyn-EGFP) into the muscle fibres of adult mice by plasmid electroporation (Gervásio & Phillips, 2005). We used fluorescence microscopy to track the newly synthesized rapsyn-EGFP as it assembled with AChRs. Rapsyn-EGFP accumulated in the Golgi apparatus. The Golgi seems to be a staging post where rapsyn first assembles with newly synthesized AChRs on their way

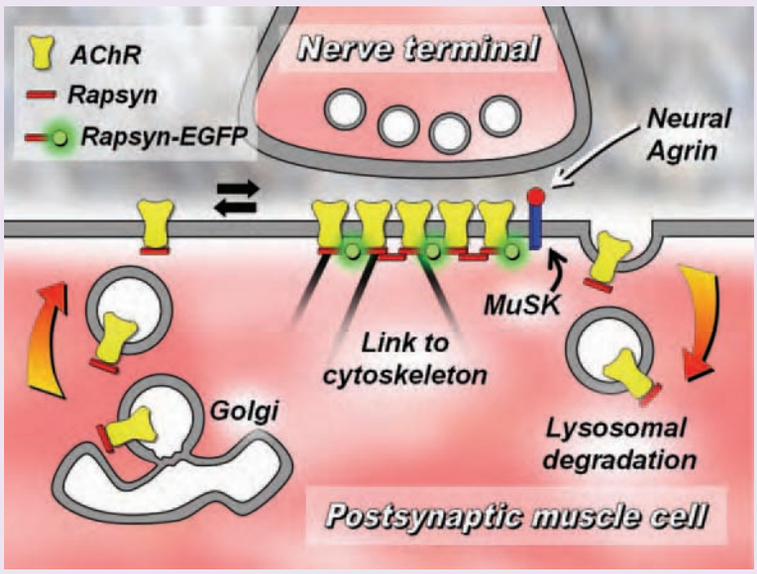


Figure 1. Rapsyn and the AChR may form a life-long partnership at the neuromuscular synapse.

to the plasma membrane (Moransard *et al.* 2003). Fluorescence Recovery After Photobleaching (FRAP) experiments suggested that, after reaching the plasma membrane, the AChR-rapsyn complex may diffuse about in the peri-synaptic membrane before it becomes entrapped in the AChR cluster (Fig. 1). Eventually AChRs escape from the AChR cluster, are internalized and are degraded in the lysosome. The half-life for survival of AChR at the synapse increases during development from about 1 day (before birth) to about 10 days in the adult rodent. Each AChR channel may form a stable (life-long) partnership with a single molecule of rapsyn (Fig. 1) (LaRochelle & Froehner, 1986).

Rapsyn-AChR stoichiometry and AChR stabilization

However, quantitative analysis suggests that the rapsyn-AChR relationship is not as monogamous as it once appeared (Moransard *et al.* 2003). Rapsyn-EGFP was able to target directly to the adult synapse, bypassing the Golgi apparatus. This nearly doubled the amount of rapsyn associated with each AChR channel. Importantly, this increase in rapsyn-AChR stoichiometry resulted in a slowing-down of the metabolic turnover of the post-synaptic AChR (Gervásio & Phillips, 2005). Over a four-day period more of the old AChR was retained and fewer newly synthesized AChRs were added to the synapse (Fig. 2). We propose that the additional rapsyn molecules stabilize the AChRs by linking them more tightly to the cytoskeleton.

Implications

Changes in rapsyn-AChR stoichiometry of a similar magnitude occur during the normal development and aging of synapses. Conceivably then, developmental increases in rapsyn-AChR stoichiometry might cause the postnatal slowing of AChR turnover at the synapse. In models of autoimmune myasthenia gravis, auto-antibodies bind AChRs, causing accelerated AChR degradation and impaired synaptic transmission. Increasing the level of rapsyn expression in the cell might offer a way of slowing this AChR loss (Phillips *et al.* 1997; De Baets *et al.* 2003). All this highlights the need to sort out the mechanisms that control rapsyn-AChR stoichiometry at the synapse.

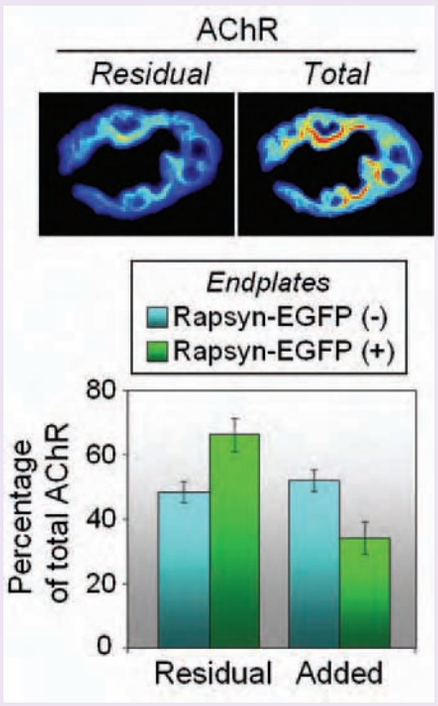


Figure 2. Artificial elevation of rapsyn-AChR stoichiometry in the post-synaptic endplate (with rapsyn-EGFP) slowed the loss of old AChRs (Residual) and their replacement by newly synthesized AChRs (Added). Top panels show residual AChRs at a synapse 4 days after labeling with rhodamine-α-bungarotoxin and total AChR (old plus new) after relabeling. Modified from Gervásio & Phillips, 2005.

Muscle electrical activity, and neural agrin, are two signals from the nerve terminal that can help maintain the ongoing slow AChR turnover characteristic of adult synapses (Bezakova *et al.* 2001). The mechanism by which they slow AChR turnover is not known, but perhaps it is by increasing rapsyn-AChR stoichiometry at the synapse.

Acknowledgements

This work was supported by a project grant from the NH&MRC, Australia and by a Sesqui R&D grant.

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Different polyamine concentrations underlie the regional difference in the strong inward rectifier K^+ current in the heart

The inward rectification of a K^+ current in the cardiac atrial myocytes is stronger than that in the ventricular myocytes. This new study reveals that different intracellular polyamine concentrations underlie the difference

Keiko Ishihara (left) and Ding-Hong Yan

In the heart, the working myocytes of the atria and ventricles are both specialised for contraction, yet show different action potential configurations. Action potential duration is shorter in atrial than in ventricular myocytes due to the steeper slope of the plateau phase (phase 2). On the other hand, the final repolarization (phase 3) is much slower in atrial myocytes due to the smaller amplitude of their strong inward rectifier potassium current (I_{K1}). Our new study strongly suggests that a difference in the concentrations of the intracellular polyamines that regulate the amplitude of I_{K1} contributes to the difference between atrial and ventricular I_{K1} in the guinea-pig heart (Yan *et al.* 2005).

The outward current through the strong inward rectifier K^+ channels is much smaller than the inward current because intracellular polyamines (spermine and spermidine) block the channels in a voltage-dependent manner. Nevertheless, under physiological conditions the outward current plays the major role, as the inward current does not usually flow at physiological voltages. In working cardiac myocytes it repolarizes the cell membrane during action potentials.

Previous studies have suggested that the amplitude of the outward I_{K1} is smaller in the atria than in ventricles not only because of a difference in current density reflecting a difference in the number of channels in the cell membrane, but also because of the stronger rectification of the atrial current – that is, the ratio of the amplitudes of the outward and inward currents is smaller in the atria. We confirmed this in guinea-pig hearts using the amphotericin B perforated-patch method, which minimizes changes in the intracellular polyamine concentration during patch-clamp recordings. Moreover, we found that the transient component of the outward I_{K1}, which is the result of competition between spermine and Mg^{2+} (a weaker blocker of outward I_{K1} than polyamines) to block the I_{K1} channel (Ishihara & Ehara, 1998; Yan & Ishihara, 2005), is only seen in ventricular myocytes. These findings raise two possibilities: either the concentration of polyamines is higher in atrial myocytes, or the atrial I_{K1} channels are more susceptible to blockade by polyamines.

The strong inward rectifier potassium channels underlying the cardiac I_{K1} are considered to be formed by homo- or heterotetrameric co-assembly of three closely-related subunits: Kir2.1, Kir2.2 and Kir2.3 (Liu *et al.* 2001). We have determined, based on its electrophysiological properties, that in the guinea-pig heart the contribution of the Kir2.3 subunit to the I_{K1} channels is very minor in both atrial and ventricular myocytes. When we tested whether the difference in the sensitivities of the channels formed by either the Kir2.1 or Kir2.2 subunit to polyamines could account for the observed difference in the outward I_{K1} in atrial and ventricular myocytes, we found this not to be the case. As one might have expected, however, increases in the polyamine concentration could change Kir2.1 currents from the 'ventricular type' to the 'atrial type' (Fig. 1). Moreover,

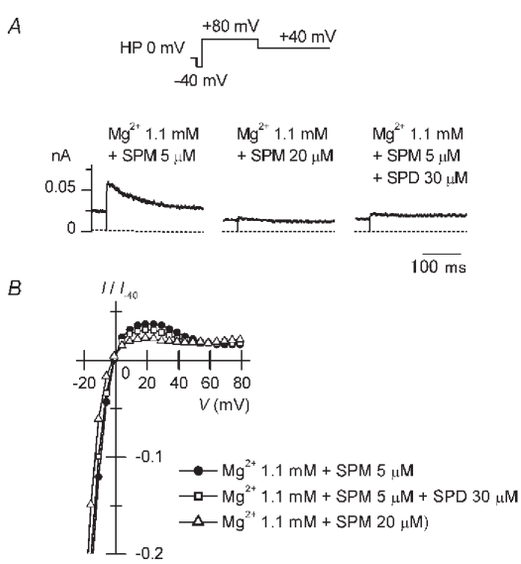

Figure 1. Effects of different concentrations of cytoplasmic polyamines on outward currents through the Kir2.1 channel observed in the presence of 1.1 mM Mg^{2+}. *A*, outward currents obtained using a repolarizing pulse protocol (*top*). An outward transient similar to those of ventricular I_{K1} flowed in the presence of 5 μM spermine (SPM) (*left*), but was nearly absent in the presence of 20 μM spermine (*middle*) or 5 μM spermine plus 30 μM spermidine (SPD) (*right*). *B*, steady-state current-voltage relationships. In the presence of 5 μM spermine (*filled circles*), a region of negative slope conductance was observed at voltages more positive than E_{rev} + 20 mV, which is also seen with ventricular I_{K1}. This region was flattened in the presence of 20 μM spermine (*open circles*) or 5 μM spermine plus 30 μM spermidine (*open triangles*), which is more like the atrial I_{K1}. Modified from Yan *et al.* (2005).

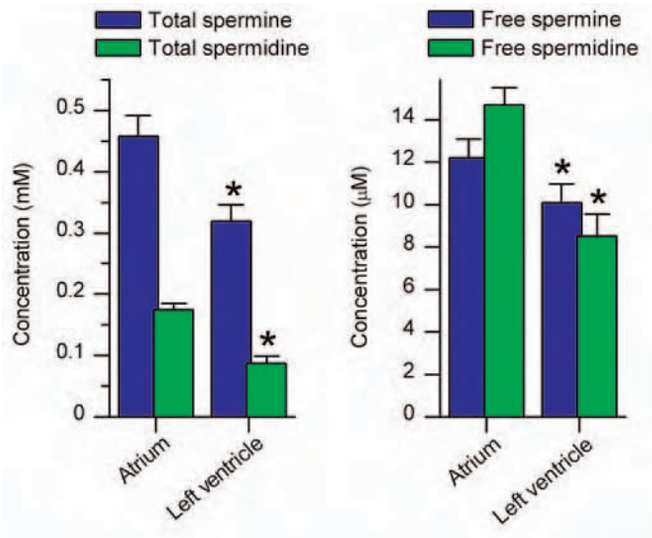

Figure 2. Total (*left*) and free (*right*) polyamine concentrations in the cardiac tissues from guinea-pig. Data are given as means ± S.D.; $n = 5$ in each group. *, $P < 0.001$ *versus* atrium. Modified from Yan *et al*. (2005).

when we then measured the polyamine contents of cardiac muscles and estimated the concentrations of total and free polyamines, we found that they were indeed higher in the atria than in the ventricles of guinea-pig hearts (Fig. 2).

Polyamines are widely distributed in eukaryotic cells, playing important roles in cell growth and differentiation, though their levels vary among different cell types (Watanabe *et al.* 1991). Our study revealed that a difference in polyamine levels contributes to the regional difference in I_{K1} in the heart. In the heart muscle, the synthesis of polyamines and their levels within myocytes are affected by a variety of physiological and pathological factors. It is known, for example, that polyamine levels are increased during cardiac hypertrophy, which may account for the observed reduction of I_{K1} that accompanies prolongation of the action potentials and the resultant increased susceptibility to arrhythmia. Thus, by regulating I_{K1}, polyamines play important roles in regulating cardiac function.

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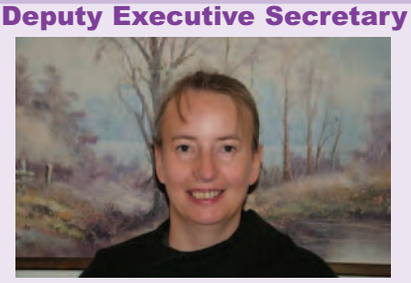
Deputy Executive Secretary



I took over from Maggie Leggett as Deputy Executive Secretary of the Society and Head of External Affairs in January.

I came to work for the Society from Brunel University, where I had a lively post as Technology Commercialisation Manager for academics with commercial aspirations. Prior to that, I had a 5 year diplomatic posting in Moscow as First Secretary Science for the British Council/British Embassy, where I forged links between British and Russian scientists in the areas of science policy and innovation development, technology transfer, science communication, and science and environmental education. Feeling so long ago now that I suspect it may have been back in the days of the Medes and the Persians, I worked for the Economic and Social Research Council on both their research management and postgraduate training sides, and The Oxford Trust, a charity set up by the famous science entrepreneur Sir Martin Wood to promote the study and application of science and technology. Here I researched technology transfer and regional economic development, and was also involved in their local science education work with Oxfordshire schools.

At university, my first degree was in Biochemistry at Lancaster, followed by postgraduate study in the area of science and technology policy in the Aston Business School, and postdoc research in the role of biotechnology in the production of food flavours and colours, and New Chemical Entity Innovation in the pharmaceutical industry.

I am thoroughly enjoying my new role with the Society, which is largely concerned with our external relations and education activities. I also wear a general management hat, assisting Executive Secretary David Sewell and helping our events, membership and grants teams. Much of my work so far has been in reviewing the way we run our operations and implementing new ways of working (with the help of the Executive Committee and Council), responding to various Government consultations, and acting as Education Officer in the gap between Sai Pathmanathan leaving and Donna Brown taking up her role.

I look forward to meeting as many of you as possible at future events.

Liz Bell

How to perform well in the heat

Athletes are aware that as the ambient temperature rises it becomes harder to perform at their peak. Mostly this is because of the problems of temperature control, fluid balance and the competition between skin and muscles for blood flow. But it is also known that, as muscles get hotter, their performance can deteriorate and they fatigue more rapidly. As an athlete one wants to know the best way to minimize the effects of heat if one is forced to compete on a really hot day; as physiologists we would like to know the mechanisms whereby increased temperature affects the performance of muscles. Our recently published paper suggests answers to both these questions (Moopanar & Allen, 2005).

Our laboratory studies the intracellular mechanisms involved in muscle fatigue. We use single fibres dissected from mouse muscles which allow us to simultaneously measure force and intracellular ions and to investigate fatigue mechanisms. A number of different mechanisms of fatigue have been identified and obviously we would like to concentrate on those mechanisms that are important to normal individuals going about their daily life or to athletes pushing the boundaries of physical performance. For instance, the popular hypothesis that accumulation of intracellular lactic acid is a major cause of fatigue does not seem to be the case in mammalian muscles (Westerblad *et al.* 2002). In a recent *Physiology News* article we summarized current ideas about the most important mechanisms limiting muscle performance for various activities (Allen *et al.* 2003).

Until a few years ago all our experiments on isolated single fibres were performed at room temperature. We did this for two reasons; one was the trivial one that it is simpler to work at room temperature. The second reason was more fundamental – that isolated single muscle fibres stop contracting after a short time at 37° C, making long experiments impossible. Recently we decided to try again to work at 37° C, since evidence was accumulating that fatigue at room temperature involved different mechanisms from those at body temperature.

When we heated our single fibres up to 37° C, we confirmed that they soon stopped contracting and when we fatigued them with repeated tetani the force declined substantially faster than at 22° C (Fig. 1). However we were aware that our colleague Mike Reid in Texas had shown that in respiratory muscles accumulation of reactive oxygen species (ROS) occurred during repeated contractions and seemed to contribute to fatigue (Reid *et al.* 1992). We therefore added a membrane-permeant ROS scavenger (Tiron) to our solutions and found, to our delight, that the muscles now survived much better at 37° C and fatigued at the same rate as at 22° C (Fig. 1).

The great advantage of the single fibre preparation is that we were able to establish the mechanism whereby force declines more rapidly at 37° C. It turns out that the calcium sensitivity of the contractile machinery declines very rapidly when muscles are stimulated at 37° C. ROS frequently convert free sulphydryl groups to disulphide bridges thereby changing protein properties. So our working hypothesis is that a protein which regulates calcium sensitivity undergoes this type of change.

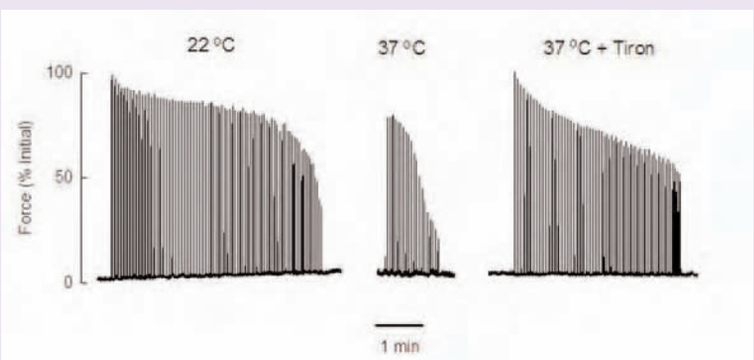


Figure 1. Fatigue due to repeated short tetani in isolated mouse muscle fibres. Force records from small bundles of mouse fibres illustrating different patterns of fatigue at 22 °C, 37 °C and 37 °C + 5 mM Tiron, a membrane-permeant ROS scavenger. The height of each vertical line represents the force of one tetanus. Tetani were continued until force had fallen to less than 50 % of the initial. Modified from Moopanar & Allen (2005).

David Allen (right) is Professor of Physiology at the University of Sydney and studies skeletal and cardiac muscle. He extends his research on muscle fatigue by occasionally running marathons. Terence Moopanar (left) is completing a PhD in Muscle Physiology and currently studying Medicine. His personal research on muscle involves body-building.

These experiments suggest that, if you want to minimize muscle fatigue at high temperatures, you might try to improve your ROS scavenging capability either by dietary methods (lots of Vitamin C and E) or by a training protocol which induced endogenous ROS scavengers. Unfortunately, current evidence on whether these strategies work or not is inconclusive (Jackson *et al.* 2004).

An unresolved puzzle is why isolated single fibres survive so poorly and are more susceptible to fatigue at 37° C. Obviously our own intact muscles work pretty well at 37° C and muscles have developed methods of scavenging ROS so that most of the time the levels of ROS are close to those which produce optimum performance. This suggests that in an isolated single fibre there is excessive endogenous ROS production and/or some of the endogenous scavenging pathways are impaired. These are areas we would like to explore in the future; together with identifying the target protein(s) and how they are modified by ROS.

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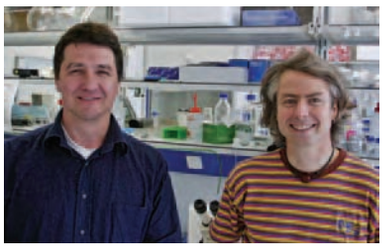
A new experimental platform for plasticity

Textbook descriptions of the physiology of memory consistently refer to Hebb's postulate that, when one neuron repeatedly takes part in activating another, the efficiency of this activation will increase (Hebb, 1949). Long term potentiation (LTP) was regarded as the manifestation of Hebb's postulate following its discovery over 30 years ago (Bliss & Lomo, 1973), and has remained the primary experimental platform for investigating the physiology of synaptic plasticity and memory. LTP studies typically use the classic brain slice experimental preparation, with single (usually extracellular) recording electrodes and the electrical stimulation of a subset of synaptic inputs. Applications of these techniques to various brain regions have revealed a surprising diversity in the conditions, which facilitate plasticity. However, the cellular mechanisms underlying the maintenance (beyond 4 hours) of changes in synaptic efficacy, that may be critical for long-term memory, remain poorly understood. While stimulus-induced gene transcription mediated by the cAMP response element (CRE) appears to play a critical role, the multitude of genes whose regulation is affected by LTP appears endless. Studies of mice with targeted disruption of genes has done little to clarify the sequence of molecular events critical for late phase LTP. Also, the brief (<8 hours) lifespan of slice preparations, and the low tissue sample volumes of single electrode work, impede or complicate most molecular analyses. Our use of a cell culture system, and the assessment of network properties as an indicator of plasticity (Arnold *et al*. 2005), must seem a radical departure from the traditional LTP assay. The advantages are obvious, however: signalling events and the expression of genes are easily monitored and manipulated in cultured neurons. The idea is that network features such as activity patterns may undergo stimulus-induced changes, perhaps long-lasting changes that may require the same set of genes responsible for late LTP or even learning and memory. Assessment of network properties can be done non-invasively, and is straightforward using an array of 60 micro-electrodes embedded into each culture dish. The observed changes were dramatic: upon a brief application of a $GABA_A$ receptor antagonist (that triggered trains of action potentials and generated robust calcium signals both in the cytoplasm and the nucleus), the network activity pattern changes from random firing to periodic, synchronized bursting (Fig. 1). This highly organized activity pattern was maintained for well over 24 hours and, most excitingly, required gene transcription taking place in a critical period of 2 hours after induction (Fig. 1).

The synchronous nature of bursting across the network implies that activity in individual neurons successfully contributes to eliciting activity in other neurons in alignment with Hebb's postulate. On a synaptic level, miniature excitatory postsynaptic currents (mEPSCs) mediated by AMPA receptors are increased in frequency, and to a lesser extent in amplitude, following induction of network plasticity. This indicates an increase in synaptic efficacy. This and several other features of LTP at synapses between hippocampal pyramidal neurons in slice preparations are also features of our new plasticity model. The persistence of bursting, like LTP, requires the activation of NMDA receptors (Morris *et al.* 1986), extracellular signal regulated kinases (ERK1/2) (English & Sweatt, 1997) as well as protein synthesis and gene transcription (Nguyen *et al. 1*994). Furthermore, activation of cytoplasmic and nuclear calcium/calmodulin dependent protein kinases and CREB-mediated gene expression are features of both models (Malenka *et al.* 1989; Bading, 2000; Hardingham *et al.* 2001). Thus, the new system may shape up as a promising experimental platform for plasticity that, given its simplicity, may facilitate the analysis of key signals such as nuclear calcium (Bading, 2000) and the search for genes important for learning and memory.



Hilmar Bading (left) and Peter Bengtson

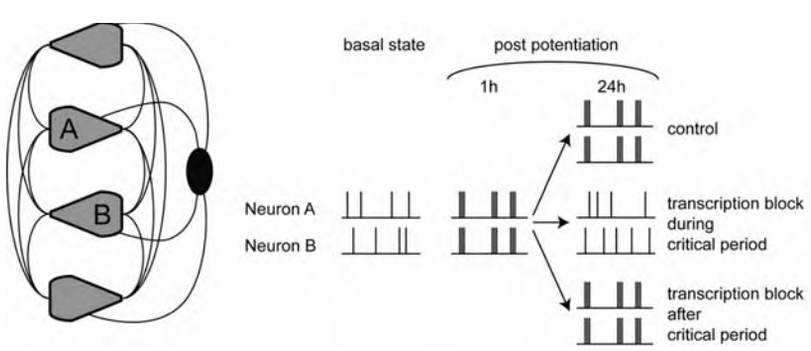


Figure 1. Shown is a schematic representation of a hippocampal culture where multiple random synaptic connections exist between glutamate (grey) and GABA (black) containing cells. The hypothetical activity of two neurons (A & B) is not correlated in their basal state, but becomes synchronized after a brief treatment. The two neurons contribute to each other's activation during this induction phase and long after due to a potentiation of their synaptic connections. After 24h, synchronized activity persists unless transcription or translation is blocked during the critical period of 2h following induction.

C Peter Bengtson
Hilmar Bading

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Spontaneous transient currents, long slow oscillations... or just wobbles?

Len Best offers a cautionary tale of the elusive nature of an electrophysiological phenomenon

Len Best – on a quest for islet cell anion channels

As a non-physiologist by training (I must admit to being a reformed biochemist) I came to electrophysiology late. But once I'd tried it, I was hooked. One of the great attractions to me of electrophysiology was that you got your results (or lack of) during the course of your experiments. You could actually sit and watch your cells doing their thing – as if still inside the body – in real time. By contrast, biochemistry (or at least the sort of biochemistry I had been doing) tended to yield results up to a week after completion of the experiment (if at all), by which time I had usually realised that I had done the wrong experiment anyway, or lost interest for some other reason. But electro-physiology was different. It was … exciting.

So approaching my, er, 'middle years', I decided to arrange a sabbatical in the lab of an esteemed pancreatic islet cell electrophysiologist – name omitted to spare him embarrassment - in order to learn enough about patch-clamping to enable me to re-badge myself and make a start in this general direction. I learned how to fabricate and fill a patch pipette, what sort of ingredients the pipette and bath solution might typically contain and how to make those all-important seals. At this point, I thought I had it cracked. This was in spite of the fact that my mentor had pointed out on numerous occasions that the main difficulty in patch-clamping was interpreting one's experimental data. After all, wasn't this true of just about everything?

In hindsight, I should have taken more heed of this sound advice. For example, it might have been advisable to begin working on a channel/current that was already well-characterised. The islet β-cell K_{ATP} channel was an obvious candidate. Adding to the already considerable wealth of information on this channel might have been the prudent option, with the added attraction of being able to talk to other electrophysiologists without them giving me funny looks and – who knows – maybe an improved chance of funding. But did I really want to be just another individual working on K_{ATP} channels? No, I would *Do Something Different*.

I had (and, to be honest, still have) a mild obsession with anion channels. I won't bore you with the background to this obsession now – maybe another time. The received wisdom among the islet cell fraternity at the time (early 90s) was that, in the pancreatic islet β-cell, chloride was at equilibrium. So even if anion channels were present in the β-cell, activating them would have virtually no effect on membrane potential or electrical activity. In any case, the received wisdom also stated that β-cells didn't have anion channels. A likely explanation for this latter notion, it now appears, is that nobody had actually bothered to look for them. So the quest for islet cell anion channels began.

But how to start? The most obvious approach at the time seemed to be to block all the other channels I could think of and see what was left. A series of bizarre pipette solutions were made up, containing no sodium, potassium or calcium. The first series of experiments would be conventional whole-cell recordings – a kind of 'catch-all' for any remaining currents. From virtually the first cell on the first day, the results were startling. Or at least, I thought so. A pattern of long, slow, transient oscillating currents of variable amplitude and duration was apparent (see Fig. 1). This was it! I had discovered a 'hidden current' and perhaps, in doing so, solved the riddle of β-cell electrophysiology! Surely, these current oscillations must play some role in determining the oscillating pattern of β-cell electrical activity? I was therefore initially puzzled that touting my prized newly-

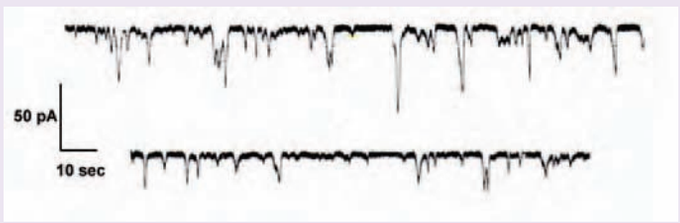


Figure 1. Spontaneous transient currents from a HIT-T15 insulinoma cell. Upper trace: conventional whole-cell recording; lower trace: excised outside-out patch from same cell. The holding potential in both cases was -60mV. Essentially similar currents were recorded from RINm5F and native rat β-cells.

obtained recordings around the lab failed to produce the anticipated excitement among my colleagues. Their reactions ranged from scepticism to utter bewilderment. The kindest remarks were along the lines of 'Where's zero current?', 'What's the reversal potential?' and 'Have you got EGTA in your pipette solution?' My initial heady enthusiasm rapidly subsided and I began to realise that these remarks were, in fact, rather helpful. Indeed, calcium-activated spontaneous transient inward (STICs) and outward (STOCs) currents were already well-documented, notably by William Large and colleagues.

But it turned out (again, I'll spare you the details) that my currents were probably neither STICs nor STOCs. For one thing, it seemed almost impossible to block them. It was also difficult to shift their reversal potential in any meaningful or predictable manner. It was suggested to me that they might represent some kind of 'seal phenomenon'. But this did not appear to explain the fact that pulling off an excised (outside-out) patch resulted in a corresponding reduction in current amplitude (see Fig. 1).

At this point, the current Editor of *Physiology News*, in a typically helpful and constructive moment, suggested the term 'wobbles' to describe my prized phenomenon. Undeterred, I presented my findings to the Physiological Society. To my great relief, among the sea of blank faces in the audience, one or two kind souls offered token questions. 'Had I tried lanthanum?' or 'Had I noted any time-dependent rundown?' Still undeterred, I attempted to obtain funding to study this clearly important new conductance. To my complete astonishment, my application was declined. And then declined again. I was convinced I must really have struck on something of Titanic importance, and I resolved to pursue the matter *To The Bitter End*.

But the bitter end came sooner than I had anticipated, and in a rather different manner. My 'wobbles' disappeared literally overnight. I tried everything. Smaller electrodes, bigger electrodes, different shaped electrodes, adding ATP, adding lanthanum, heating the lab up, playing Led Zeppelin[1] at top volume while attempting seal formation – but nothing.

Then, in an idle moment, I suddenly realised that the disappearance of the spontaneous currents had coincided with a seemingly minor change in the composition of our cell culture medium. Specifically, we were now using a new batch of fetal calf serum, having recently run out of our long-term favourite Canadian vintage. (Actually three bottles left in the freezer by a long-departed previous lab neighbour).

So it would simply be a matter of obtaining more of the Canadian elixir, or at least finding a viable alternative. Well, no. In fact, neither option yielded any success whatsoever. The Canadian vintage was long sold-out, and no other fetal calf serum did the job. Wobbles weren't just inexplicable – they were ephemeral too. And now they were lost in perpetuity.

Well, not quite. To rub salt into the wound, my aforementioned sabbatical mentor later revealed to me during a bar session at an islet cell workshop that his lab too had observed 'The Wobble Phenomenon'. 'And', he intimated 'it was in one of the very best islet cell preparations we have ever made'.

A large drink (or several) seemed to offer the only possible consolation.

Len Best
Department of Medicine, University of Manchester, UK

P.S. It now turns out that chloride is not at equilibrium in the β-cell. And these cells express at least two types of (real!) chloride channel. But that's another story. And I still have an unfinished manuscript on the 'Wobbles' in my bottom drawer ...

[1]*Dazed and Confused*, since you ask

TRP CHANNELS: UNIQUE PLAYERS IN CELL FUNCTION

Huis Van Chièvres, Leuven, Belgium
15-17 September 2005

This international symposium, will bring together leading scientists working on transient receptor potential (TRP) channels and cover molecular and functional aspects of most known TRP channel subfamilies.
The symposium will take place in the Huis Van Chièvres (pictured above) in the 'Groot Begijnhof' (Great Beguinage), one of the best preserved beguinages (a residence of the female followers of the Beguine religious movement) in the world and declared as a UNESCO World Heritage Site. The full symposium programme is available at:
http://kuleuven.be/trp2005/

Contact: Bernd Nilius or Annelies Janssens at:
annelies.janssense@med.kuleuven.ac.be

PHARMACOLOGICAL INSIGHTS AND THERAPEUTIC TARGETS IN HEART FAILURE

Christ Church, Oxford, UK
18-20 September 2005

Full details available from the British Pharmacological Society:
meetings@bps.ac.uk

LARGE ARTERY STRUCTURE AND FUNCTION

Institute Océanographique, Paris, France
30 September-1 October

This 2 day meeting will focus on the methods of assessing arterial stiffness and pressure wave reflections and their applications to clinical practice; epidemiological aspects; structural and functional regulation of large arteries.
http://www.artery.ukevents.org

JOINT SCIENTIFIC MEETING OF THE GERMAN PHYSIOLOGICAL SOCIETY AND FEPS

Munich, Germany
26-29 March 2006

This meeting is the next in the series of FEPS meetings in association with national societies. Contact: Ulrich Pohl at:
physio2006@med.uni-muenchen.de

Additonal Noticeboard listings appear on p. 51

Committee of Heads

The 8th Committee of Heads of Pharmacology *Hot Topics* meeting was once again held at the excellent venue of the University of Manchester's Chancellors Conference Centre on 19-20 April.

This was also, for the third year, run jointly by the Pharmacological and Physiological Societies and the meeting was hosted by Clive Orchard (new Chair of Committee of Heads of Physiology) and Brenda Costall (Chair of the Committee of Heads of Pharmacology). As a new venture, the meeting started before lunch on the Tuesday, with the business being conducted over two half days, rather than packed into one, as previously. This seemed to work well, with a relaxed schedule and no premature rush for trains, planes and automobiles to get home, as in previous years!

The first session of the afternoon was on *Translational research* (TR), with the subtitle *Sexy title for preclinical and clinical pharmacology*? While many of us probably thought that this is exactly what TR is about, i.e. 'advancing molecules into medicines', Donna Johnstone (Discovery Medicine Director (Cancer and Infection) at AstraZeneca), described how TR is designed to make 'go/no go' decisions much earlier in the drug development process than hitherto. TR pulls together a wide range of technology platforms such as genomics, proteomics, genetics and functional imaging for the identification of drug target actions, which can then be applied in the clinic as a 'biomarker'. Again acceleration of the process is achieved by going straight into volunteers to look for effects on the specific biomarker, before patient involvement. At the heart of effective TR is enhancing industrial/academic links, particularly in the form of seconding clinical fellows into industry and placement of postdocs into the laboratories of leading academics who are developing the biomarkers to be used in patients. Donna also explored the attributes required of a translational scientist: in essence, the individual has to be a generalist, not a specialist (reminiscent of what was once described by Gaddum as the 'Jack of all trades' nature of the pharmacologist). Skills needed include good scientific and technological knowledge; ability to link between laboratory work and the clinic; ability to interpret clinical data; and excellent interpersonal and communication skills across disciplines. The possession of *in vivo* skills by graduates (or at least a willingness to be trained) was also considered a positive attribute.

Following Donna's highly illuminating presentation and the opportunity for further discussion after tea, we returned to a two hour session on *How can we keep young people in academic research*? This was kicked off by presentations from two young lecturers (Caroline Dart from the University of Leicester and Morgan Denyer from the University of Bradford). Although their paths to permanent lectureships had been rather different, as might be expected, there was considerable commonality in their observations concerning the road to independence, from a post-doc to becoming a lecturer. Very telling was Caroline's observation that, in 1979, there were 6,000 contract research staff (CRSs) in UK universities. By 1996 this had increased to 33,000, but was accompanied by a mere 2% increase in academic posts. It was commented that research council and charity fellowships were not well matched to the typical training of a post-doc, i.e. after a couple of post-doc positions, an individual may be too old for an intermediate fellowship, but it is much too soon for a senior fellowship. The RCUK Fellowship scheme will probably go some way to alleviate this, but it is early days yet. Although both speakers came across as obviously enjoying academic life, when thinking about 'why academics leave', they highlighted the pressures within their own institutions to perform; non-transparent, tortuous career progression; increasing administrative and teaching loads and a general lack of time.

The feedback from the deliberations of the subsequent break-out groups, yielded some frank discussion. Fundamentally, it was felt that there is no real problem with keeping young people in academic research – the stellar, highly motivated post-docs will always get positions. However, there is a major problem with there being too many post-docs in relation to current and likely availability of permanent academic posts. It was also considered that universities support post-docs very poorly. Typical of the many similar comments included:

- We know that 9 out of 10 post-docs will not get permanent academic positions. Are they in denial?
- Many post-docs do not realise that they are not good enough and academics are not good at telling them;
- In some areas there is a real shortage of good post-doc candidates to fill lectureship positions;
- Post-docs need to hit the ground running from day one – few do;
- Post-docs need to take responsibility for their own career development;
- If post-docs are not stellar during their first position, they should be out;
- Need to open the eyes of PhDs to other careers, and post-docs that are not going to progress to academic careers need to be assisted with pathways out of academia.

There the first day's business ended and we were treated to an excellent dinner followed by a highly illuminating and amusing after-dinner reminiscence by John Fozzard (Novartis).

Day 2 began at a civilised 9.30 a.m. with pretty serious stuff: *Full Economic Costing* (or FEC). If my experience at Bristol is typical, most HoDs will have had presentations, fora, and workshops *ad nauseam* on this vital, but intrinsically dull, topic. So, expecting to drift into a stupor, at the prospect of three presentations, it was a pleasure to have these bad thoughts confounded. Steve Visscher (Executive Director, BBSRC), Jim Port (JM Consulting, who designed the TRAC methodology which highlighted how all universities were making a deficit on research, however funded), and Mike Collis (Pfizer and ABPI Academic Liaison

Committee) each gave talks of great clarity. While the mechanics of FEC are now fairly clear (it needs to be, with just the summer before implementation), where I suspect most of us lacked knowledge was how the pharmaceutical industry would approach FEC. The ABPI has very reasonable concerns about defining what constitutes industrially supported academic research that is 'in the public good' and that which is not (the latter to attract 100% overheads). Mike Collis indicated that a 'one size fits all' model would not work; that there was not an industrial pot of gold out there, and (apart from contract research, which pays the going rate) there needed to be a flexible and realistic approach to industrial funding, whereby reasonable overhead costs would be paid for collaborative research projects. The pharmaceutical industry already contributes a great deal in direct funding of studentships and fellowships (almost £62 million in 2003) and makes other substantive contributions in the form of access to technologies and novel compounds, intellectual input and large numbers of student placements (both graduate and undergraduate). Mike entered a plea that the Research Councils should not apply FEC to CASE studentships; the consequence of this would be to drive down volume. There was also a need for the Research Councils to significantly increase their contribution for consumables, as this was currently completely inadequate.

There was considerable discussion and questioning (some decidedly sceptical) of the three speakers. Some of the key points raised – though there are no definitive answers yet, included:

• Is there going to be sufficient money, and will the volume be maintained?

• How is postgraduate training going to be addressed? This isn't likely to happen very rapidly as it will cost hundreds of millions to fix;

• How will charities fund the indirect element in the long-term? What will be the longevity of the Charity Partnership Fund which is designed to meet the shortfall?

• How will cost differences between institutions (estates costs in particular, including, for example, costly high-maintenance animal facilities) be addressed? We were reassured that these costs would be met, since there were obvious historical differences between institutions. However (the sting in the tail), there would be pressures for efficiency and harmonisation! It was commented that there were already 'benchmarking clubs' between some institutions to enable costing comparisons to be made. It was clear that the data which will be accumulated by the Research Councils will not be made available to HEIs;

• EU funding? The government is reportedly exerting increasing pressure for there to be FEC applied to all its grants;

• Teaching? We are told that FEC is on the way for this sphere of our activities also. This is logical considering that the TRAC exercise identified the extent to which teaching cross-supports research. There was some concern that HEFCE might interpret this as their being an over-funding of teaching. However, the evidence suggests that this is not the case since teaching/research activities are so intimately interwoven.

So we came to the end of another year's very informative and sociable *Hot Topics* event. Many thanks go to the excellent speakers and, of course, to our local host Arthur Weston, and the staff of Chancellors. No doubt we'll be back there again for more hot stuff in Spring 2006.

Peter Roberts
Secretary, Committee of Heads of Pharmacology

Physiology To the Limits!

As part of Science Week, the Department of Physiology, University of Cambridge, opened its doors to the public for an afternoon of 'hands-on' physiology. There was a range of experiments and demonstrations on offer from modified undergraduate practicals to research projects. Around 300 innocent visitors braved the 80 steps up to the Physiology Teaching Lab. On arrival, some were fingerprinted and then subjected to a battery of tests from measurements of blood pressure, peak flow, heart rate and fitness. Further round the laboratory, already excited children were stimulated further – electrically! Next to them others were placed on a spinning chair whilst wearing black hoods – fortunately the only reflex evoked was nystagmus. Interestingly, parents looked on, apparently without fear, whilst we did all of this and their children twitched and flinched in unusual ways.

After 2 hours of Key Stage 1 ECG, Christof (above) is not looking his best. Gwen Tolhurst (below) persuades a child that ulnar nerve stimulation won't hurt! Part of the Physiology Teaching Lab in full flow (bottom). (*Photos by Roger Thomas)*

All of this fun would not have been possible without the cooperation of two sets of physiologists. Firstly, members of the department – technicians, undergraduates, post-graduates and academic staff – gave up their time to speak about physiology for three solid hours in ways that engaged both toddlers and grandparents alike. Secondly, members of the Physiological Society indirectly supported this event through a grant from the Society. Thank you!

I just wanted to feed back to you how much my children enjoyed the Science Week event in the physiology lab on Saturday. Of all the events we went to, they pronounced the Physiology event the best! I think this is largely because of the enthusiastic and non patronizing way that you spoke to them while outlining the basis for the ECG. As my 8 year old daughter said afterwards, 'I can't decide whether to be an astronomer or a physiologist now – I just feel inspired!!' ***Joan J***

Christof Schwiening
Department of Physiology, University of Cambridge, UK

Under Your Skin...

Sai Pathmanathan reports on the head-to-head between Gunther von Hagens ('The Plastination Professor') and Robert Winston ('The Fertility Lord') at the recent Cheltenham Festival of Science

A year or so before starting work at the Physiological Society, I was sent a free ticket by the British Interactive Group (www.big.uk.com) to attend Gunther von Hagens' *Body Worlds* (*Körperwelten*) exhibition at the Atlantis Gallery in London. The words *Decide for yourself* were scribbled on the ticket envelope. I'm not one of those wimpy, squeamish types, so I decided to check it out – I really had no idea what to expect.

The exhibition attendees that day were mostly non-scientists (I gathered this by screams of 'eugh, is that what happens to your lungs when you smoke?') and a lot of artists sketching various body parts. This was just an art gallery with amazing eye-catching exhibits. I felt I was looking at weird robots on display carrying out very human actions: for example, playing chess or sports. One specimen was kneeling as if praying to the gods above. By the side was a plaque with a small dedication to all those wonderful people who had donated their bodies for the exhibition. Then it hit me. To me this was now a room full of dead people. I could see dead people. *Real* dead people. People who once upon a time breathed, dreamt, sang, danced, hopped, skipped and jumped.

As many of you already know Society Member, John Lee co-presented *Anatomy for Beginners* on Channel 4 with Gunther von Hagens (see interview in *Physiology News* **59**, 21). This programme was the perfect form of public engagement. Despite a number of complaints (mainly before it was aired), the programme achieved record viewing figures and much positive feedback. The general public are a nosey lot. This was the ultimate reality show.

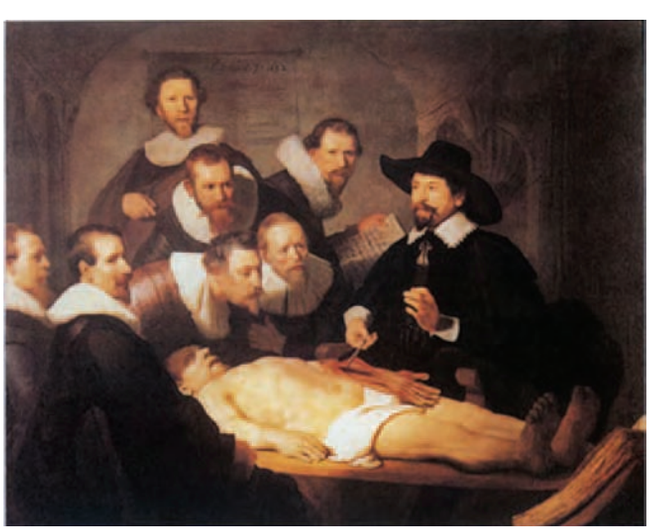
On 8 June 2005, at the Cheltenham Festival of Science, Gunther von Hagens (with his trademark hat) and Robert Winston (with his trademark 'tache) took part in a session called *Under Your Skin* sponsored by Channel 4. As *TimesOnline* put it: Dr Death v Lord Life.

Gunther von Hagens began his presentation with a video clip of the *Body Worlds* exhibition for those who were not familiar with it. He explained the history of past anatomists, his plastination empire, first specimens and the actual process. His eyes seemed to light up when he spoke about how this process allowed him to put the specimens in very life-like positions. I suppose that by arranging the specimens in life-like poses, Von Hagens has made it less distressing for those without a medical background to appreciate what the human body is all about (full details of *Body Worlds,* and how plastinates are formed, are available at www.bodyworlds.com).

In London, he said, over 800,000 people visited the exhibition, with 50,000 visitors in the first 20 days, and even now all over the world the exhibition is visited by millions. Is this not just a travelling circus? Von Hagens disagrees. Although he calls this Event Anatomy, he stresses the educational value. According to the opinion polls, only 2% of exhibition attendees thought it was a bad exhibition. Polls by different institutions showed that, after attending, over 80% of attendees wanted to know more about the human body and 45% said the exhibition made them think more about life and death.

His work offers the opportunity for everyone to compare healthy and diseased tissue, and much more; for example, the study of disfigurations of fetuses before, during or after birth. His specimens also allow medical professionals to study high quality dissections and view intricate anatomical details from all angles.

Gunther von Hagens describes himself as a scientist and an inventor. Inventors are creative, so he thinks of himself as the bridge between art and science. It is only because of the nature of his work that it falls under the banner of science. It seems that he does see this as an art form more than a science. And I couldn't help but think he's a very good



Gunther von Hagens wears his hat out of respect for Dr Nicolaes Tulp (made famous in Rembrandt's *The anatomy lecture*, pictured above.

business man – just browsing the souvenir stands at the exhibition is enough to reinforce this. It's a nice little earner. Is this why people doubt the morality of his exhibition?

He finished off by saying that he wears his hat out of respect for Dr Nicolaes Tulp (made famous in the painting *The anatomy lecture* by Rembrandt). And he smiled (the first time I had ever seen him smile).

Robert Winston then began his presentation. He asked: is this exhibition science, anatomy, education, art, just a business, or a public offence? He quickly followed this with an important fact: Dr Tulp got forearm anatomy completely wrong. It was obvious Robert Winston was not a Von Hagen fan.

He showed slides depicting various specimens from the exhibition. One was of a man on a trapeze. Like many of us, Lord Winston agreed that this was indeed a very skilful dissection, with the skin cut away in sections to reveal the muscle beneath. But then went on to add that the specimen didn't give us any information about the muscles' function and therefore would not be helpful in a medical school.

Winston said he had reviewed the exhibition for BBC Radio and said that the visitors he questioned were not interested in it at all and that they hadn't learnt much about how their body worked. He then added that a child's book of physiology and a perusal of Gray's Anatomy would be more informative. (Yes, perhaps more informative, but extremely boring).

He also believes that the exhibition isn't science at all. If the exhibits added to the knowledge of mankind, it could be classed as science. There is no focus in the descriptions, no clear delineation of what each organ does, so how can it be educational? Is it art, then? Winston thinks it is to a certain degree, and would rather look at these bodies than a pickled sheep in formaldehyde. But then stated that art needs imagination and this clearly had no imagination. He concluded his argument by saying that Von Hagens' work is mainly trivial.

The footballer – by arranging the specimens at the *Body Worlds* exhibition in life-like poses, Von Hagens has made it less distressing for those without a medical background to appreciate what the human body is all about. But Robert Winston feels the specimens give no information on the muscles' function and would not be helpful in a medical school.

A dialogue between the two speakers followed. Gunther von Hagens responded to Robert Winston's comments about the lack of educational value. He mentioned that the Index of Plastination reveals publications where plastinates have been used in university teaching and this list speaks for itself. Winston did not agree. He asked why we need plastinates when there are a huge variety of specimens all accurately labelled, i.e. those at the Guy's Campus and The Royal London, which have been more than sufficient for many medical students. He then went on to say that modern science has to be aware of the community at large, or else we run the risk of making scientists look arrogant. Von Hagens responded that he was proud, not arrogant. All he wants is to show people who want to know, what their body is all about. The Plastination Professor mentioned the 'democratisation of bodies/anatomy' several times, which the Fertility Lord picked up on: 'What does this democratisation mean? It's just a buzz word to get attention.'

Whilst both professors sat arguing, neither of them looked arrogant. Both simply agreed to disagree.

The audience participation was perhaps the best part of the whole session. We were asked how many would volunteer our bodies for plastination. Out of about 200 people in the audience, only 3-4 hands went up. Some said they wouldn't mind offering their body for medical research, but not plastination. The subject of religion came up, i.e. that many religions believe the soul is the most important part of our existence, so why do we treat the body as sacred? It is as though we wish to keep it untarnished (non-dissected) for sentimental reasons – not that we'd know; we'd be dead!

Another participant said that Robert Winston was privileged to have cut up corpses as a medical student. She, however, was not interested in going to medical school, but is still fascinated by the things going on under her skin. The audience applauded her comments. Winston advised she should buy a copy of Gray's Anatomy, to which she replied, 'It's not the same.'

The true feelings of the public are unclear. It seems that the popularity of the exhibition (based on ticket sales) is purely a result of the public's curiosity (caused by media hype) and not an actual need to be educated. Winston did admit that there was a little bit of education (i.e. you could indicate where the liver is). But overall that this was super-entertainment. Those who do agree that the show is worthwhile are in two minds about offering their own bodies, as they would need to think about their relatives' feelings. Some even made comparisons to the Alderhey scandal.

An elderly gentleman then stood up and grabbed hold of the microphone. He said he was a clinical anatomist and a fan of Von Hagens. He truly believes that medical schools are depriving students of dissection time and therefore plastination is going to play an important role in the future.

This was a fascinating debate and, whilst I'd like to take sides, I actually find myself agreeing to points made by both 'Dr Death' and 'Lord Life'. Oh, and Von Hagens also said he's looking forward to his own plastinated body being put on display after his death. I think I'll give that show a miss.

Sai Pathmanathan

The Journal of Physiology

Dominique Debanne

Dominique is Director of Research, Neurobiology of Ion Channels at the Institut National de la Santé et de la Recherche Médicale (INSERM) in Marseille, France. He studied with Yves Frégnac (Paris) and Beat Gähwiler (Zurich) and, since 1998, his research group in Marseille has investigated the cellular rules and mechanisms of intrinsic plasticity that depend on the regulation of ion channels. His current research interest is centred on synaptic transmission in the CNS, short-term synaptic plasticity, activity-dependent synaptic plasticity (spike timing-dependent plasticity, LTP and LTD), epilepsy and intrinsic plasticity.

David Grundy

David joined the faculty at the University of Sheffield in 1980 and is currently professor in Biomedical Science. His research, funded from research councils, industry and charities, focuses on 'neurogastroenterology', a term which encompasses the regulation of gastrointestinal function by neural mechanisms. While the approach is largely basic science, a strong clinical element aims to understand the basis of sensations such as nausea and discomfort arising in both functional and organic GI disorders. The applied aspect also extends to collaboration with industry, looking at afferent transduction mechanisms as potential therapeutic targets.

Toshinori Hoshi

Toshinori is an Associate Professor in the Department of Physiology at the University of Pennsylvania School of Medicine, Philadelphia. His research interests include ion channel gating and modulation, oxidative stress, protein oxidation and aging.

Jimmy Zhou

Jimmy Zhou is Associate Professor in the Department of Physiology and Biophysics and Department of Ophthalmology at the University of Arkansas in Little Rock. His current research interests cover cellular physiology and synaptic circuitry of the mammalian retina and spontaneous retinal activity and visual system development.

New Editors appointed

Nine new Editors joined the Editorial Board of *The Journal of Physiology on* 1 July – Dominique Debanne, David Grundy, Toshinori Hoshi, Michael Kotlikoff, Chris Peers, Nelson Spruston, Jennifer Van Eyk, Håkan Westerblad and Jimmy Zhou. Brief biographies of some of them appear on this page.

A number of Editors also retired on 30 June – Mark Donowitz, Michael Duchen, Rodolphe Fischmeister, Vadivel Ganapathy, Stefan Heinemann, Stephen Jones, Yoshihisa Kurachi, José López-Barneo, Amy MacDermott, Richard Miles, Richard Moss, Stewart Sage,* Ann Silver and Ger Stienen. The Editorial Board is very grateful to them all for the important contributions they have made to *The Journal of Physiology.*

(*In our next issue Stewart Sage reflects on his time as Chair of the Editorial Board).

Publication news

It's that time of year again – the 2004 impact factors (IFs) are out. *Experimental Physiology* Editors can congratulate themselves on an increase in the IF from 1.220 in 2003 to 1.881 and a rise from 51st to 33rd in the physiology journals table. The Editorial Board will reflect on how to build on this improvement at their forthcoming meeting in Bristol. *The Journal of Physiology* has remained steady at 8th place in the table (7th last year) with an IF of 4.346 (4.352 last year). Measures put in place in 2004 to reduce the acceptance rate, and thereby reduce the number of uncited papers, should show an effect next year.

Society members who access *The Journal* via the Society website will be familiar with the HighWire Press home pages. HighWire allows journals to customize their website home pages, and the *J Physiol* Editorial Board has initiated a review of the home page. A user group has been set up to contribute ideas to this process. Have you ever wondered what the logo on the left was about? Here's what one user thought about it: 'Is it a dog? To tell you the truth, I thought it was some kind of bird. And I didn´t realize until now that it was related to Phys Soc'.*

Why not have your say? Any Members who regularly read *The Journal* via HighWire, and are interested in the way journals are presented online, are welcome to join the group. Please contact me at chuxley@physoc.org

Jennifer E Van Eyk

Jennifer is an Associate Professor of Medicine, Biomedical Engineering and Biological Chemistry at Johns Hopkins University, Baltimore and Director of both the Hopkins NHLBI Proteomic Group and the Hopkins Bayview Proteomic Center, with a mandate to facilitate proteomics applications in medicine. Her research laboratory studies the underlying molecular mechanism of heart and lung disease using proteomic methodologies, for use as potential biomarkers for the diagnosis, prognosis and risk stratification of heart disease.

Michael Kotlikoff

Since 2000, Michael has been chair of the newly formed Department of Biomedical Sciences at Cornell University and organises the Cornell Mammalian Genomics Initiative. He currently directs the Cornell Core Transgenic Mouse facility, serves on several national and international committees and is a member of the Vascular Cell and Molecular Biology Study Section at the NIH. His research interests include smooth muscle and cardiac muscle biology, particularly the regulation of Ca^{2+} release, and the development of tools for *in vivo* imaging and muscle lineage tracing.

Håkan Westerblad

Based at the Department of Physiology and Pharmacology, Karolinska Institutet since 1992, and awarded a full professorship in 2003, Hakan has a long-standing interest in cellular mechanisms of skeletal muscle fatigue. A new focus of his research team is on functional studies in skeletal and cardiac muscle of mouse disease models, with a specific interest in mechanisms underlying muscle dysfunction in mitochondrial myopathies and glucose transport in relation to type 2 diabetes.

The next *Journal of Physiology* symposium, advertised in this issue, will focus on endocrine mechanisms and the placenta. The symposium takes place on Thursday, 17 November at the 3rd International Congress on Developmental Origins of Health and Disease at Toronto (http://www.mpi-evv.com/2005DOHaD/framset.htm). Papers from the symposium will be published in *The Journal of Physiology* as early as possible in 2006. Anyone currently preparing a research paper on a related topic is invited to submit the paper to *J Physiol* for inclusion in the symposium issue. Related papers will be peer reviewed in the usual way and should be submitted by 1 December 2005.

Carol Huxley

(*The short history which follows may shed some light)

The Society's 'mascot'

(reprinted from Chapman R. *The Physiological Society Magazine* 1994 **14**, 11)

The Society's Dog has been attending our Scientific Meetings since 1942 when Sir Henry Dale gave it to the Society. This means that nearly 20 Honorary Meetings Secretaries have had the responsibility of looking after it. All must have experienced the horror of thinking it had gone walkies. After all, it had been given a Dog Licence for the Würzburg City Council so to do, when its deputy (remember the rabies legislation) attended a Joint Meeting with the Deutsche Physiologische Gesellschaft. Sadly, at the recent Meeting in Bristol this year (1994), what had stalked many a Meetings Secretary became a reality – the Dog was stolen along with the car of one of the Society's employees.

The Dog was given to Dale by Sir Charles Sherrington who had received it from the Dutch physiologist Rudolph Magnus. It was supposed that it had been made by Magnus' father, but Dale later corrected this with the statement that 'the Dog was of unknown origin'. This led the then Secretary, Bill Paton, to comment that 'the Dog was not good enough for Crufts'. Like

all past Secretaries, I have a special fondness for the Dog, especially as my wife and I established that the Dog had almost certainly been made during the Renaissance. This discovery started when one of us (not a physiologist) saw a littler mate in the Louvre during the Joint Meeting with L'Association des Physiologistes in Paris. Consultation with the experts confirmed the Dog's pedigree but also revealed that the origin of these fine dogs is a matter of debate. Weihrauch had suggested that they originated from the Dürer revival which started in Nuremberg around 1600; Wixom had tentatively assigned them to Innsbruck and the last quarter of the 16th century, while Iona Cairns noted that some had been made for the French Court later in the 17th century. We presented these findings to the Society at the Edinburgh Meeting in 1989 (*J Physiol* 1990, **420**, 100P).

In an attempt to recover our strayed Dog, its photograph and details have already appeared on the HTV *Police 5* programme and in the *Bristol Evening Post*, along with the offer of a £1,000 reward for information that leads to its retrieval. The Dog's details have also been entered on a national computer database that searches all catalogues of auctions of antiques. Although bronze dogs of this type are rare, ours is easily recognised because a previous Secretary had two holes drilled in its behind so that it could be mounted on a plinth.* This feature will be critical to any identification and should assist Members browsing antique shops and fairs in the hope of increasing their research funding.

Editor's notes:

The original Dog was never recovered, but a replacement was cast from the mould used to make copies for retiring Officers of the Society, and continues to preside at Society dinners.

*The Dog acquired its plinth during Denis Noble's tenure as Meetings Secretary. After Trevor Shaw's sudden death, Denis took over supervision of one his research students, Brian Blood. Brian, in addition to being a physiologist, was an excellent musician (tenor recorder) and had married into the Dolmetsch family. Their skills in making high quality musical instruments were brought into play to craft the plinth in gratitude. The base of the plinth was 'turned' just as one would for making a woodwind instrument. The Dog and plinth (an artist's impression of which appears above) were displayed for the first time at a Committee dinner, where the addition of the plinth received mixed reactions due to a perceived mismatch between the style of the dog and the period (Victorian) of the plinth.

Experimental Physiology

Great news

At its board meeting in Bristol the editors of *Experimental Physiology* were delighted to learn that the impact factor had risen to 1.88, as far as we know the highest it has ever been. This was against the tide of happenings with other physiology journals, the impact factor of many of which had decreased. *Experimental Physiology* is currently the fastest rising journal and our plans for the future are designed to maintain this. Its mix of hot topic reviews, symposia articles, prize lectures and original papers is proving very attractive.

Part of the reason for this is that the journal is now available, and read, worldwide and thanks have to go to Blackwell Publishing for increasing its exposure, as well as to authors, for the increasingly higher quality of submissions. Furthermore, the recent introduction of 'exchange of views' articles has raised a great deal of interest. These will continue. Coming soon are themed issues on *Modelling of biological systems* (edited by Peter Hunter) and *Neural control of circulation during exercise* (edited by Peter Raven). Original papers in these areas are welcome. Many other areas of physiology are also covered. Remember *Experimental Physiology* is a publication of the Physiological Society, so please support it by submitting your original work on integrative and translational physiology.

John H Coote

Chair of the Editorial Board

THE JOURNAL OF PHYSIOLOGY

SYMPOSIA

Endocrine mechanisms Placenta

Thursday, 17 November 2005

at the 3rd International Congress on Developmental Origins of Health and Disease, Toronto, Canada

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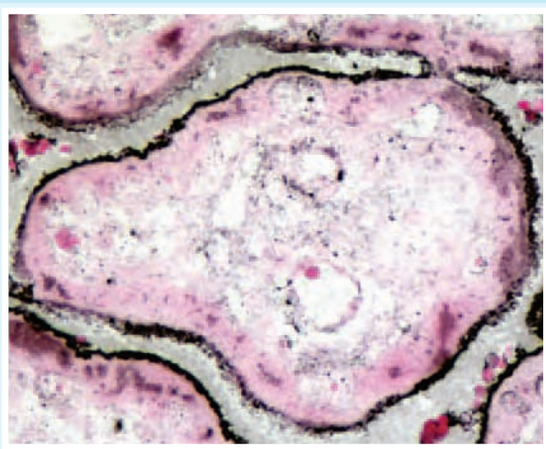
Endocrine mechanisms



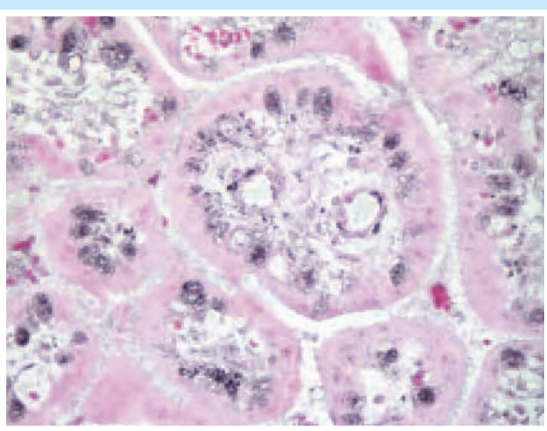
Participants:

Stephen Matthews (Toronto, Canada)
Fetal experience and neuroendocrine function and behaviour after birth

Jonathan R Seckl (Edinburgh, UK)
Glucocorticoid programming of the fetus: an exceptional or common mechanism?

David Phillips (Southampton, UK)
Fetal programming of the biological responses to stress

Placenta



Participants:

William Hay Jr (Denver, USA)
Regulation of fetal metabolism and development by changes in placental nutrient transport to the fetus

Leslie Myatt (Cincinnati, USA)
An active role for the placenta in fetal programming

Abigail Fowden (Cambridge, UK)
Programming the placenta

The Journal of Physiology is published by Blackwell Publishing on behalf of the Physiological Society in 24 fortnightly issues in eight volumes. For further information go to **www.jphysiol.org**

Blackwell Publishing

Teaching of *in vivo* research techniques in UK universities – wide-ranging and prompt action is needed

Less than 2% of UK graduates in physiology, pharmacology and related subjects are now taught whole animal *in vivo* skills, despite a high demand for this expertise. A recent survey by the British Pharmacological Society (BPS) and the Physiological Society looked at the UK-wide state of affairs and offered some possible ways forward

Background and methodology

The British Pharmacological Society (BPS) and the Physiological Society represent over 5,000 scientists, the majority of whom are active researchers in UK universities. Both Societies have Members who use animals as an essential part of their research programmes, and so have been aware for some time of the problems associated with *in vivo* research and teaching (*In vivo* Pharmacology Training Group (2002). The fall and rise of *in vivo* pharmacology. *Trends in Pharmacological Sciences* **23**, 13-18). Furthermore, other countries are experiencing similar situations (French ED (2004). Academic pharmacologists: confronting new challenges in educational programs of graduate and health care professionals. *J Pharmacol Exp Ther* **309**, 441-443). Whole animal *in vivo* research is a critical component in progressing biomedical advances, in utilising the data generated by the genome project and in developing new medicines and treatments for disease. It is also a regulatory requirement before new medicines can be tested in humans. Finally, it is important to ensure that the vital animal research that UK scientists need, and for which there is no alternative, is done to the best scientific and welfare standards.

A study by the BPS in 1997 was one of the first to show a serious decline in the number of departments able to provide hands-on teaching programmes in this area. Whilst use of videos and computer simulations are commonplace, and play an important role in biomedical sciences teaching, feedback from final year students typically cites the importance of relevant practical classes in influencing decisions on future careers. This realisation led to the initiation of a collaborative project between the BPS and all the major UK-based pharmaceutical companies, whereby 10 departments teaching these skills received partial funding for consumables, etc.

A later survey, undertaken by the Association of the British Pharmaceutical Industry (ABPI) in 2003, identified a significant skills shortage in graduates and postgraduates with whole animal skills. This stimulated more cooperation between the pharmaceutical industry and learned societies, and subsequent collaborations involving the Physiological Society and BPS have involved the setting up of vacation courses for students at universities where this *in vivo* teaching is not available. Most recently, a well-publicised BPS industrial academic fellowship scheme has been initiated, where top-up awards are available to institutions receiving new blood lectureships, academic fellowships and PhD studentships in physiology, pharmacology and toxicology.

Despite these initiatives there is continuing concern that the number of graduates with whole animal skills is declining. Furthermore, even the current situation is not sustainable as the age of university lecturers able to teach these skills is increasing without adequate provision for replacement. The two Societies therefore agreed to contact their respective Heads of Department Committees with a short questionnaire to determine the current numbers of students who receive a hands-on education in animal research techniques, and the age profile of those able to deliver it.

Results

Replies were received from 43 universities (see Table below). Approximately 25% of the universities offer *in vivo* training where undergraduate students hold their own licences. Of a total population of over 8,000 graduates of physiology, pharmacology, biomedical or biological sciences in any one year, only about

Table of Survey Results

Criterion	Total
Number of institutions responding to the survey	43
Number of departments able to offer *in vivo* courses where the undergraduate holds their own licence	11
Total number of academics able to teach these skills	194
Total number of these academics who will retire in the next 5 years	56
Technicians able to assist with research/teaching involving animals	50
Total number of these technicians who will retire in the next 5 years	11
Total number of students per year taught physiology, pharmacology and related subjects in these institutions	~ 8000
Approximate numbers of students/year who are taught *in vivo* skills as part of their degree	122 - 150
Approximate number of students/year who receive exposure through placements, vacation courses etc	35 - 82
Number of students/year who graduate without any exposure to these skills	~ 7800

120-150 per year will graduate with these skills having been taught as part of their degree course. In addition, some exposure may be available via demonstration classes, research projects which require students to obtain a personal licence, or industrial placements. The latter two options are only available to a small subset of graduates, however, and the number taking these options varies annually. This means an overwhelming majority of graduates in pharmacology, physiology or related subjects have no direct exposure at all to *in vivo* techniques.

The situation is set to deteriorate. As part of the survey, universities were asked for the age profile of academics and technicians qualified to teach or demonstrate *in vivo* skills. Over a quarter of academics falling into this category retire in the next 5 years, leaving less than 150 able to teach the next generation of *in vivo* researchers. Many of these academics work in research-intensive universities, and may therefore not spend a large amount of time teaching. Approximately the same percentage of technicians will also be retiring.

Reasons cited for decline in teaching

Institutions were asked to comment on why they were no longer teaching *in vivo* skills for which there is obviously a demand. The main reasons listed were cost, bureaucracy and inability to replace retiring staff who could teach in this area. Several stated that courses had been stopped within the last 10 years. A list of individual responses to the survey are given on p. 41.

Financial problems were broken down into the cost of facilities/animals for this type of work, the cost of obtaining a personal licence for, sometimes, just one practical session, and the high teacher/student ratio required. The BPS's support of courses was referred to several times, with institutions commenting that without this they would no longer be able to offer the courses. Practicals involving animals require a large amount of space per student, and the pressure for higher research output, which had led to conversion of teaching laboratories into research areas, was also cited. The high teacher/student ratio means that for many universities *in vivo* teaching simply is not cost effective. These institutions have responded to demands to increase intake numbers and this has been at the expense of teaching of this nature.

Specific quotes regarding bureaucracy referred to discouragement from individual Home Office Inspectors regarding the chance of obtaining an educational licence, and difficulties in persuading local ethics committees of the need for educational project licences.

Several institutions cited problems recruiting suitably qualified academics to fill these vacancies. One pointed to the change in emphasis over last 20 years towards research using reduced biological systems (e.g. cell-based studies) resulting in staff with these skills replacing whole animal biologists (see *Individual responses*). Therefore, even if a university intended to keep whole animal courses running, when the relevant teachers retire it might be impossible to replace them.

Conclusions and recommendations

Less than 2% of graduates in physiology, pharmacology and related subjects are now taught whole animal in vivo skills, despite a high demand for this expertise from industry. This percentage is set to fall as universities struggle to find the money to fund this type of teaching and to cope with the bureaucracy. With more than a quarter of academics able to teach these skills retiring in the next five years, it is unlikely that even those universities wishing to retain the expertise will be able to recruit suitably qualified staff. Urgent action needs to be taken to avoid an imminent escalation of the skills shortage in this area. We suggest that existing collaboration between industry and learned societies is built upon, and that the learned societies, the research councils, biomedical charities and HEFC should work together to address this crisis.

Concrete suggestions are:

• the high costs of essential animal facilities and of obtaining Home Office Licences should be supported by HEFC and other university funding agencies;

• the Home Office should be made aware of the need for these skills among graduates, and be more receptive to educational licence applications;

• a strategy needs to be developed to increase the awareness of *in vivo* techniques to undergraduates as part of their course and to provide *in vivo* skills training to a greater number than currently receive this. This strategy will require the re-building of an *in vivo* teaching skills base in a number of university departments and could include:

a) grants to release some time for those academics nearing retirement to pass on skills and techniques to younger colleagues;

b) an increased number of 'ring-fenced' *in vivo* research studentships and fellowships to provide the academic teachers of the future, with incentives such as enhanced stipends and consumables budgets;

c) new academic positions to reverse the decline in teaching *in vivo* skills at the undergraduate and postgraduate level so that the capacity is increased by ~50% from its current level.

• universities should review the skill set of their physiology/pharmacology/biomedical sciences graduates, and explore means of providing some exposure to *in vivo* research. This would require funding;

• the results of this survey and earlier ABPI studies should feed into the current review of careers provision in schools. If school children obtain an improved understanding of the use of animals in medical research, and possible careers in this area, they are more likely to choose universities able to provide this teaching.

Maggie Leggett

Individual responses to the survey

Some of the problems foreseen with continuing teaching in this area included:

'*Big problems already. Cost mostly, both in cash and time. Staff are keen to carry on, but costs are very high. Not to mention the bureaucracy in getting the licences, delays, etc.*'

'There are very few labs and therefore pre/post docs being trained in in vivo *techniques/integrative physiology and pharmacology. Therefore, unless this is addressed immediately, with the ageing population of people trained in these techniques, within 5-10 years it will be impossible to offer such teaching even if all other barriers (cost, licences, etc.) were removed. Furthermore, in the current climate of budgetary constraint, whilst such teaching has significant educational benefits, the inevitable small class sizes and the high cost of both animals and specialist equipment make it hard to justify, particularly if equipment required cannot be borrowed from research labs.'*

'*Problem:*
• loss without replacement of appropriate teaching staff with whole animal experience; process attributable to change in emphasis over last 15-20 years towards research using reduced biological systems;
• university management directed by cost considerations favouring less expensive courses in biology;
• administrative burden of, and hostile attitude towards, Teaching Licences.'

'The delays (6-12 months) associated with obtaining licenses, certificates, animal ethic committee approvals and attendance of animal handling courses make teaching integrative physiology very difficult.'

'It is becoming a problem to find young academic staff with integrative expertise; we are relying more than hitherto on medical demonstrators and on one staff member who is an active clinician. Two staff retire in the summer and filling the teaching gaps is difficult.'

'The number of academic staff with the appropriate skills has decreased over recent years – probably more worrying is the decline in technical staff with these skills.'

'Enormous problems. A large proportion of the good systems in vivo *pharmacologists or physiologists I know/have known are nearing retirement (or have retired/died).'*

'We have already had to give up in vivo *teaching because the staff with the relevant skills are too busy with other teaching. We have one member of staff who has held education project licences previously. All of our academic and technical staff who could contribute to* in vivo *teaching are ~50 apart from one young lecturer (~30) who does not have a permanent contract.'*

'Many of the academics holding personal licences in our department have virtually ceased to use them. Very soon the ageing population of staff with appropriate experience will mean that we are unable to sustain this form of teaching.'

£11 million for Capacity Building Awards in integrative mammalian biology research

A unique new partnership between research and higher education funding councils, learned societies and a consortium of pharmaceutical companies* has established an £11 million dedicated fund to springboard capacity building in integrative mammalian biology.

Integrative biology is the study of how gene products integrate into the function of whole tissues in intact organisms. Understanding gene function in mammalian systems ultimately requires the use of mammalian models. The information generated is central to the development of new therapeutic approaches to tackle human and animal diseases and to help deliver safe and effective medicines.

The Capacity Building Awards (CBAs) have been pioneered as a response to concerns, highlighted by recent surveys (including that co-authored by the Society and reported on the previous pages), that the UK is losing capacity in integrative mammalian biology. The CBA partnership will provide resources to rebuild this capacity to ensure that the UK can capitalise on the wealth of data generated by large scale genome projects for the development of new therapeutic approaches to tackle human and animal diseases and the delivery of safe and effective medicines.

CBAs will support institutions that already demonstrate existing strengths in integrative mammalian biology to enable them to equip the next generation of researchers with the range of expertise and skills required including best practice in the use of animals in research, high quality experimental design and the application of a broad range of techniques and approaches in integrative mammalian biology.

The partnership is now calling for Expressions of Interest (www.bbsrc.ac.uk or www.mrc.ac.uk) by 26 September 2005. Capacity Building Awards are open to all UK HEIs with an established record of research and training in integrative mammalian biology.

Julia Goodfellow, BBSRC Chief Executive, says: 'Research into integrative mammalian biology is absolutely fundamental to help us to translate the huge amount of information from human and animal genome projects. Only by bringing together this unique range of funders will we develop the truly integrated approach to build capacity in this area and place it on solid foundations for the future.'

Colin Blakemore, Chief Executive of the MRC, says: 'This will give an immediate boost to integrative mammalian biology research capacity. The MRC is delighted to provide research funding for this important initiative. It is in everyone's interest to consolidate and strengthen these research skills in the UK. The pharmaceutical sector in particular needs trained physiologists and pharmacologists to help to turn scientific knowledge into advances in prevention, diagnosis and treatment.'

***Members of the new partnership are**:

Research and higher education funding councils and learned societies: Biotechnology and Biological Sciences Research Council (BBSRC), Higher Education Funding Council for England (HEFCE), Medical Research Council (MRC), Scottish Higher Education Funding Council (SHEFC), British Pharmacological Society (BPS)

Pharmaceutical companies: AstraZeneca, GlaxoSmithKline and Pfizer

Deceased Members

The Society reports, with regret, the deaths of David McKie Kerslake, OBE (Yateley, Hants) and Robin H Hooper (Loughborough). Obituaries may be carried in a future issue of the magazine. Other obituaries appear on p. 48.

Members' honours, awards and promotions

Nancy Rothwell FRS (pictured above), MRC Research Professor at the University of Manchester, has been made a Dame Commander of the Order of the British Empire in the Queen's Birthday Honours List in recognition of her work on brain injury and stroke and her contributions to science administration.

When *Physiology News* caught up with her, Nancy said she had been 'totally stunned' by the news, which arrived in a letter from Number 10 Downing Street. 'It said "the Prime Minister is minded to ... and if the Queen accepts …" and so on … so [at the time] it wasn't certain' she says. 'I had no idea I had been nominated for anything.'

Speaking on behalf of the Physiological Society, President Alan North commented:

'The Society is delighted to learn that Nancy Rothwell has been honoured. All in the Society will take great pride in the occasion, and we offer her our congratulations. The honour doesn't simply reflect Nancy's substantive contributions to original research in the areas of the control of body fat metabolism, and inflammation and injury in the central nervous system. It also recognises her life-long commitment to two further important causes. The first is making science accessible to a broad range of the public, and particularly school children. The second is an honest and open commitment to the use of animals in medical research, combined with a leading role in reducing, refining and replacing their use wherever possible.'

Another tribute to Nancy came from past Physiological Society President, and current Head of the MRC, Colin Blakemore. Colin also highlighted Nancy's work in science communication, calling her 'a role model for young people'. In a statement on the MRC website he too touched on Nancy's work defending animal research, praising her 'courage in debating difficult and controversial issues'. The charity *Research into Ageing*, which has supported Nancy's research, said they had 'no doubt that [Nancy Rothwell] has been instrumental in changing attitudes [to animal research]'.

So what does being Dame-d actually entail? Nancy jokes that 'The term Dame hardly conjures up exciting images of Sir Something-or-Other riding on a white horse with an avenging sword. Dame is rather more Pantomime! (below). But if it helps to get people to recognise science I'm all for it – and it's probably very important for the charities I represent.' There may be other more subtle benefits, though. 'I hear it's good for getting the best seats in restaurants and on planes!'

So what is the proper form of address for a Dame? Apparently 'Professor Dame Nancy…' is correct, but Nancy says she is hoping she will only get called that '..for a few official duties. I hope everyone who knows me well will be aware that I prefer neither Professor or Dame, but Nancy. That's what the cleaners call me.'

Austin Elliott

Nancy Rothwell (right) shows off her barbecueing skills at the staff party. The lettering on her hat reads 'DAME'

Ernie Wright (University of California, Los Angeles), above, and **David Gadsby** (The Rockefeller University, New York), below, have been made Fellows of the Royal Society.

The following promotions take effect at University College London in October:
John Carroll (Professor of Reproductive Biology)
Lucie Clapp (Professor of Vascular Physiology)
Mark Farrant (Reader in Neuroscience)
Michael Gilbey (Professor of Integrative Neuroscience)
Bruce Lynn (Professor of Physiology)
Margaret Mayston (Senior Lecturer)
Angus Silver (Professor of Neuroscience)
Lucia Sivilotti (Reader in Pharmacology)
Geraint Thomas (Senior Lecturer)

Recent Society activities

Council met recently at UCL to discuss a number of issues. Alan North was re-elected at the meeting to stand as President for another year, and Prem Kumar was elected to succeed Bridget Lumb as Meetings Secretary. On a sad note, we said goodbye to several members of Council who stepped down - Rod Dimaline, Michael Rennie, Daniela Riccardi, Richard Vaughan-Jones, Jeremy Ward and Stan White. Stewart Sage also left Council as his term of office as Chair of the Editorial Board of *The Journal of Physiology* came to an end in June.

It was agreed that the Physiological Society would continue to strongly support the Biosciences Federation, and we have agreed to increase the level of our membership subscription. Mike Withnall, Chief Executive of the Federation, is currently based in the Society's London office and an update on its activities appear on p. 44.

Future strategy, governance, and organisational issues also formed a major discussion item. To keep in step with increasingly rigorous Charity Commission requirements, the Executive Committee has proposed that all members of the Society's Council should be Trustees, with Council gradually reduced in size from 26 to 20 members over a period of 2 years. This proposal is to be brought to the Annual General Meeting in Bristol. At the time of writing, the result of Members' voting is not known.

The activities of the London and Cambridge Offices have been reviewed to implement new improved ways of working, including the creation of new Events, External Relations and Education, Grants and Membership Services Teams. The contribution of the Society's Officers to the work of the Society, particularly the significant time they spend on administration was noted, and their current close involvement considered vital. Committee structures were also reviewed, most subcommittees being left essentially unchanged, but Council approved the creation of a new External Relations and Education Subcommittee, and a new Membership Services Subcommittee, from the former External Relations and Education and Membership Subcommittees. The new subcommittees will take effect from Autumn 2005.

Concerning the healthy finances of the Society, Council noted that the move of our journals to Blackwell Publishing had led to an increase in income, but that potential developments in the area of open access publishing needed to be carefully monitored. Where Members are concerned, the Society is implementing improved methods of credit control to handle debtors.

It was noted that Society Meetings appeared to be going from strength to strength, with our main Meeting in Bristol in July hosting the Federation of European Physiological Societies (FEPS), and Focused Meetings scheduled for the University of Oxford and UCL in September and December 2005 respectively. On our international horizon, workshops scheduled for 2006 will take place in Caracas, Kiev and Prague (dates to be confirmed), and Council applauded the efforts of David Eisner, Bridget Lumb, and Alan North whose sterling work resulted in the Society successfully bidding to host the IUPS meeting in 2013.

David Sewell
Liz Bell

Parliamentary and Scientific Committee

Giovanni Mann, the Chairman of the Society's Executive Committee, and I attended the Parliamentary and Scientific Committee AGM and dinner on 23 May.

Ageing is a fascinating topic and we were not disappointed, hearing presentations from Tom Kirkwood, (University of Newcastle), John Lever (Imperial College) and Reynold Greenlaw (Oxford Computer Consultants). Tom reviewed current research on the biological basis of ageing and age-related diseases, John the biomechanical aspects of ageing, and Reynold some of the latest technological solutions to problems associated with Parkinson's rehabilitation.

Tom Kirkwood explained that life expectancy has increased over the decades in an almost linear fashion. Is ageing a clock? Apparently not, as in the wild, animals do not generally get very old, and organisms have not evolved a programme for ageing. We are programmed for survival not death. Is it due to genes? Statistically, long life does run in families with genes accounting for maybe 25% of observed longevity. Is ageing caused by damage?

There appears to be strong evidence for this with longevity being affected by the effectiveness of our cellular repair and maintenance mechanisms, and the extent of our exposure to damaging agents. The bad news is that damage by reactive oxygen radicals and other toxic agents begins early in life and our repair mechanisms probably only evolved to keep us going for about four decades at the most. Is it our food? This is probably significant, since mice and rats on reduced calorie diets live longer. Rising levels of obesity in the human population are a cause for concern, since random molecular damage is affected by stress, environment and poor diet. He concluded by observing that the hope is to exploit the malleability of the ageing process by decreasing exposure to damage, and by improving nutrition, lifestyle and environment.

John Lever explained that many of the overt symptoms of ageing are caused by bioengineering changes. Ageing in external appearance is caused by changes in the structure of our elastin and collagen fibres. Formation of elastin ends at puberty, but collagen continues to be replaced, for example in wound healing. The way ahead? Cosmetic surgery is only superficial, we need to learn how to protect critical organs. It is hoped that we will eventually be able to control the balance between connective tissue formation and degradation, perhaps through tissue or genetic engineering introducing cells programmed to produce elastin.

Reynold Greenlaw reviewed ways of controlling the symptoms of Parkinson's disease. Death of brain cells leads to a drop in the neurotransmitter dopamine, resulting in the classic symptoms of slow movement, rigidity and tremors. The major current treatment is pharmacological, drugs such as L-Dopa. However, some non-pharmacological approaches can also deliver surprising results. It has been observed for a long time that acute emotional, visual or other triggers can stimulate movement, the paradoxical kinesis response, and the EU have funded a project prototyping potential technical aids. Some of the prototype virtual reality devices simulating the triggers for patients have had remarkable success in restoring mobility, and will be entering clinical trials in 2005 to 2007.

As ageing affects everybody, a lively discussion ensued after these seminars and around the dinner table between the scientists, Lords and MPs present. One Lord observed that it is something of naturally pressing concern to the aged members of their House. It is not clear when or how the linear increases in longevity will grind to a halt. Current generations are noticeably younger at each stage than their forebears, but this effect may be reversed in the younger generations, who are increasingly likely to be obese, have a poor diet, and take insufficient exercise. There is cross-party support for taking these issues seriously and trying to plan ahead for the effects on Society and the Economy.

Liz Bell

BIOSCIENCES FEDERATION

Value for money

An update on the activities of the Biosciences Federation from Mike Withnall (left)

It is now almost 6 months since the Biosciences Federation accepted an invitation from the Physiological Society to share accommodation at its London offices. This is an opportune time to remind Physiological Society Members of what the Federation actually does, particularly since the Federation's activities are largely funded by a levy of £1 per head (£1.50 from 2006) on each full Member of a Federation organisation! The provision of office facilities is just one expression of the strong support that the Federation receives from your Society.

I believe that Physiological Society officers are very keen for the Federation to be successful because they recognise the need for the biosciences to have a powerful unified voice in the same way that chemistry and physics have the Royal Society of Chemistry and the Institute of Physics. The type of influence that these bodies exert takes years to build up, and needs considerable resource, but the Biosciences Federation can point to some notable successes. Since its launch at the end of 2002, the Federation has been particularly strong in responding to science policy consultations from bodies such as parliamentary committees, the research councils and funding councils. The Federation's written evidence has frequently been quoted in the reports of these consultations, and in the past year the Federation has been invited to give oral evidence on strategic science provision in universities and on climate change.

The Chief Executive of BBSRC approached the Federation early in 2005 to suggest regular meetings between the two organisations to discuss matters of common interest. One of the major findings of a survey of heads of university bioscience departments that the Federation carried out in late 2004 was a strong dissatisfaction with the balance between directed projects and responsive mode grants funded by the research councils. When BBSRC was shown the survey, its findings were added to the agenda of a meeting for heads of academic departments already planned by BBSRC for April, and the Federation was invited to attend. It is pleasing to note that BBSRC's spending plans for 2006-2008, announced at the end of May, include a 4% a year increase in responsive mode funding.

At the beginning of May the Federation was invited by the Director General of the Research Councils to provide the Department of Trade and Industry with case histories of fundamental research discoveries in the biosciences that have been successfully translated into products or services that have benefited the health and wealth of the nation. We understand that the information is to be used to demonstrate to the Prime

Minister's policy advisers the value of continued investment in the science base. The Federation has provided nine case histories, covering topics from DNA fingerprinting to breeding 'super broccoli' enriched in a cancer combating compound.

The examples above show the Federation responding to invitations for action; two examples of the Federation being proactive are the drafting of a report on the top science policy priorities for the new Government, and the establishment of a working group to address how the biosciences can avoid the problems of university course closures experienced in recent years by the physical sciences. The Federation consulted member organisations in order to define priorities for the former and, not surprisingly, addressing recruitment and retention issues in academic bioscience came top. A Parliamentary launch for the report is planned for the autumn. The working group concluded at an early stage that its focus should be on enthusing young people with the excitement of the biosciences as they proceed through all stages of their education, so that there is not a demand problem. In this case evidence for the working group's report was obtained from a consultation of stakeholder groupings having an interest in the outcome of bioscience education. It emphasises the importance of curricula focusing on core principles rather than excessive detail, and being linked to issues in everyday life; the crucial importance of practical and field work; the need for assessment to reward skills and the application of knowledge rather than regurgitation of facts; the vital imperative of providing quality careers advice before secondary students choose subjects; improved dialogue between 6th-form teachers and university lecturers; and for teachers and lecturers to have access to high quality continuing professional development What is likely to grab headlines is a call for standard attainment targets (SATs) to be abandoned in their present form because they encourage narrow teaching to the test and distort curricula. This report will also be launched in the autumn, and copies sent to all the major education decision-makers.

Further information about the activities of the Biosciences Federation can be found at www.bsf.ac.uk

One of the issues discussed in the report is the need to find new ways of encouraging young graduates to visit schools to explain to students why they find bioscience so fascinating. I know that the Physiological Society is keen to involve its young Members in this project, which we intend to action through the Federation's Education Committee.

If the Biosciences Federation is to become a unifying force for the biosciences, then it needs to promote liaison between bioscientists. For member organisations the Federation provides an opportunity to contribute to science policy papers, while the monthly science policy digests, and quarterly newsletters (both of which are posted on the web) keep people informed of, what is happening nationally and within the Federation. We rely largely on parent societies trickling information down to the grass-roots membership. The Federation's Animal Science Group (ASG) and European Liaison Group (ELG) provide excellent examples of reaching out to their communities – both have members or observers from a range of charities, research funders and industry. The Education Committee, too, includes representatives covering all aspects of education (e.g, school teachers, Centre for Bioscience of the Higher Education Academy).

Members of the Physiological Society may well be aware of the activities of the ASG and of the Education Committee, but less familiar with the European Liaison Group. It was established because members of the Federation Council realised that UK bioscientists are frequently taken by surprise by European Union legislation that affects them. Discussions with some of the larger charities and research councils found them to be in the same boat. The Federation thus co-ordinates a meeting of organisations intended to keep an oversight on matters emerging from Europe so that each knows what actions others plan, and with an intent for joint action where appropriate. Topics considered over the past year include the proposed European Research Council, the Clinical Trials Directive, changes to regulations dealing with the use of animals in research, better medicines for children, REACH chemicals testing legislation and the implications for schools of regulations restricting the disposal of animal waste. A digest of European news is posted at the Federation's web site.

I hope you agree that the Federation is doing useful things, is beginning to make an impression, and represents good value for money even when the subscription fee is increased in 2006. It is a very lean operation – the activities are carried out largely by just three part-time staff and with the goodwill of member organisations that allow their staff some time to help the Federation.

Mike Withnall
Chief Executive, Biosciences Federation

Merger news

Cambridge, UK: After a great deal of persuasion and discussion, and two votes by the staff, the Departments of Anatomy and Physiology have agreed to merge. The two departments will be run together informally for some months while the Statutes are rewritten, with full merger probably being effective from January 2006. The new Head of the merged department will be Bill Harris.

Oxford, UK: After brief discussions and no votes the Medical Science Division Board announced that, from 1 October, the Physiology and Human Anatomy and Genetics Departments will merge, with Sir George Radda as the new Head of Department.

Erratum

Ellaway PH. Ten papers on motor control that have been tough acts to follow. *Physiology News* **59**, 18.
Final reference should read: Barker D, Emonet-Denand F, Laporte Y, Proske U, Stacey MJ (1973). Morphological identification and intrafusal distribution of the endings of static fusimotor axons in the cat. *J Physiol* **230**, 405-427.

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NewScientist

The Physiological Society

THE BIOCHEMICAL SOCIETY Founded 1911

gsk GlaxoSmithKline

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society for general Microbiology

How BIG is your question?

These days in science there seems to be an awful lot of emphasis on things being big.

To be a true success, it seems, you have to be big in every way. It helps to be a Big Lab (big both size-wise and figuratively). And if you yourself are not Big yet, it helps if you have trained in a Big Lab. You need big friends, certainly as collaborators on your grant proposals and preferably on the funding panel as well. You will have to have at least one Big Publication (i.e. one in a Big Journal, preferably Nature, Science or Cell). It seems to help if you are in a Big Department (see above), and it also helps to be in a Big University.

The other thing that has to be BIG is your question.

As one ex-Head of Department of mine put it in a speech (or tirade, if you prefer) to the Department's graduate students:

'I don't want us to be a Department of meek little electrophysiologists lurking in their own little holes… or people who only care how much sodium is in rat wee… I want people tackling BIG QUESTIONS.'

The same gentleman was fond of asking people, in appraisals or even just in the coffee room, what their Big Question was.

In Departmental shorthand, Big Question soon became abbreviated to 'BQ'. No relation to B & Q, you understand, but just BQ, also handily standing for 'Bulls**t Quotient'.

A Big Question, it transpires, is the grand concept (conceit?) that means you are working on SOMETHING REALLY IMPORTANT. Curing cancer, or heart disease, or neurodegeneration, or similar.

It also helps to be able to sum up your BQ in a catchy line.

For instance:

'We're solving how vascular smooth muscle relaxes - it's all about the endothelium'

'Modulating Kimr4.9 channels: a key to rewiring neuronal excitability'

'Modifying in utero programming of adult disease – neonatal intervention for lifelong health'

Or even that old standby:

'Developing potential new therapies for stroke/heart failure/chronic pain/whatever'

As with the last one, sometimes these lines are so generic that they can be used again and again, like:

'Optimising gene therapy for [insert pet disease]: a key step to restoring function'

Or the simple but achingly contemporary: 'Towards stem cell therapy for [insert pet disease]'

All of these, you will admit, have a pretty high BQ factor - whatever you think BQ stands for.

The point being that it's not so much about what you do, but about what you can dress it up as.

Well, no big surprise there.

However, there is a problem with BQs. They tend rapidly to become bandwagons (BWs), mopping up funding, the attention of the best labs, and the best postdocs and students, who understandably want to be in on something Big. This goes along with the modern taste for targetted funding, focused initiatives and so on.

Whether it produces better science, let alone the end-point that the BQ tag-lines above (many nicely honed for the titles of grant applications, note) point to is another question.

Most scientists seem to believe, when you get right down to it, that it is difficult or even impossible to predict in advance which discovery is going to prove to be important 10 or 20 years down the line.

Which suggests that meek little electrophysiologists, or indeed people piddling about with rat wee, are just as likely to discover something significant as million-dollar labs devoted to solving neurodegeneration, or whatever.

It just won't appear in such a high-impact journal. Or get the grant renewed.

And this brings me to my end-point: surely what is important is to do good, careful, science, making sure that you do it as well as you can at the time, and then publishing it with as little spin, hype, exaggeration, call it what you will, as possible. Maybe it will prove important; more probably it won't. That's life. But at least you will have done your job.

As the great Richard Feynman once wrote to an ex-student worrying about the insignificance (as he saw it) of the research problem he was working on: "The worthwhile problems are the ones you can really contribute something [towards solving]. No problem [in science] is too small or too trivial if we can really do something about it".

In other words, just find a question.

And remember:

Size isn't everything.

Mark Cain

Donald Hume Steven

1933 – 2005

Donald Steven MA Vet MB FRCVS, and Fellow of Churchill College Cambridge, died on 4 May after a courageous 40-year battle against multiple sclerosis. He was born in Plymouth where his father worked at the Laboratory of the Marine Biological Association. At the beginning of the War Donald and his brother were evacuated to the Scottish Borders where they were beaten up at school on account of their English accents; their Scottish accents earned them the same fate on their return home.

Donald developed an interest in the history of biology and medicine after reading communications by Robert Hook and Leuwenhoek (and many others) in a facsimile edition of the *Philosophical Transactions of the Royal Society* in the science library at his Bristol school, Clifton College. This interest was strengthened by the wealth of early scientific writing he found in the Anatomy and Zoology libraries when he went up to King's College, Cambridge to read Zoology. In his Editor's Preface to *Comparative placentation: essays in structure and function* (1975) Donald wrote that he was prompted to read veterinary medicine by an illustration in Thompson's *Elementary Veterinary Science*, reminiscent of the work of Ruini [1530–1598, an Italian anatomist]. While seeing practice as a veterinary student he was introduced to fundamental problems of placental structure and function. On his appointment in January 1961 to a Demonstratorship in Veterinary Anatomy in Cambridge he put this interest aside, but later, under the guidance of Robert Comline in the Physiological Laboratory, he began to investigate the vascular anatomy of the placenta in the sheep and mare. Donald was a superb artist; this meant that his papers and abstracts were beautifully illustrated, as was his teaching material. But he brought more to his teaching than knowledge and draughtsmanship – he brought imagination and memorable humour. In the dog, sweat glands are largely confined to the footpads: who could ever forget this after seeing Donald draw paw prints across three black boards to illustrate a dog walking on lino on a hot day? The life-sized cardboard cut-out of a model in a Playtex Living Bra, which enhanced his demonstration on the cow's udder, is still used by the Department of Anatomy. In Donald's day, though, the vets were taught in the Sub-department of Veterinary Anatomy, of which he was Director from 1984 until ill-health and deteriorating eyesight forced his early retirement in 1989.

Donald's early interest in scientific history made him the ideal choice as the Physiological Society's first Archivist when, in the 1970s, it was decided to establish an Archive in Cambridge at the Churchill College Archives Centre. He held this position until the Archive was moved in 1990 to the Contemporary Medical Archives Centre at the Wellcome Foundation in London. In his role as Archivist (marked on his retirement by the presentation of a bronze replica of the Society Dog), Donald served as a Designated Member of the Society

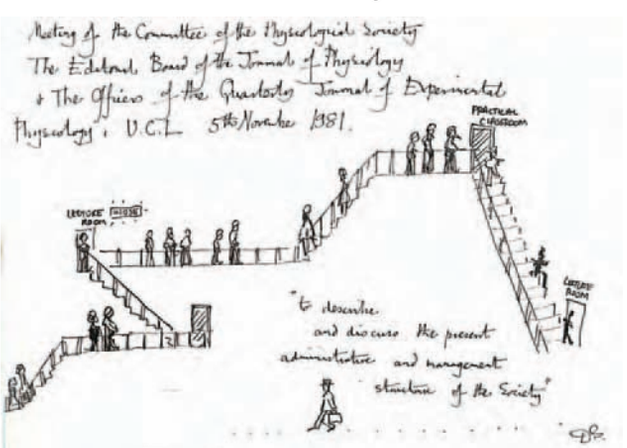


Figure 1 (below left). Members of the Society's Committee and *The Journal of Physiology* and *Quarterly Journal of Experimental Physiology* Editorial Boards search for a space for a discussion.
Figure 2 (above). Jim Pascoe 'hoist with his own petard'.

Committee from 1980 to 1982. Once again his sense of humour and artistic talents came to the fore, enlivening (or defusing) many a Meeting. The two figures show typical examples of Donald's vignettes. Figure 1 dates from November 1981: it commemorates one of the occasions when the relationship between the Committee and the Editorial Boards of *The Journal of Physiology* and the (then) *Quarterly Journal of Experimental Physiology* was not all sweetness and light. The Boards took the view that they did the work while the Committee spent the money. Tim Biscoe, as Society Secretary, was keen to improve the situation by bringing all parties together for a soothing discussion in the Physiology Theatre at University College London. Unfortunately, he didn't know the Theatre was in use by another department, the Department of English no less. This meant we had to trail up to the large old practical classroom where, perched on hard stools, Board Members and Committee Members confronted each other across the laboratory benches. Geoffrey Burnstock, realising that this arrangement was inherently uncomfortable, and not conducive to intelligent discussion, offered us space in the old Anatomy Lecture Theatre – and, as Donald captured so accurately, off we trailed again. Figure 2 records the Committee Meeting in Bristol in February1982. Jim Pascoe, in excellent form, was generating considerable heat. It was a very warm room so he leapt up to open the window but unfortunately caught his foot in the window cord – another moment that was faithfully recorded. Donald was also renowned for relieving the tedium of Examiners' Meetings by providing cartoons of some

of the more bizarre information in the exam scripts. The statement that 'cows should not be fed on turnips in case they came out in the milk' inspired a picture of turnips plopping from the udder into the bucket, to the surprise of both cow and milker. To illustrate the claim that without a special layer, horses' hoofs would come off in the rain, Donald drew a hoof flying off the leg of a wet, and completely hoofless, horse that was saying 'Damn, there goes my last one.'

Donald will long be remembered for his contribution to the Physiological Society, his inspirational teaching and artistic abilities, and his kindness, stoicism and humour. It was fitting that a family dog attended his funeral: many of the large congregation recalled their vision of Donald, pipe in hand, his bow tie at an angle, and his current beagle beside him. Our sympathy goes to his wife, Sue, and to his children and grandchildren.

Ann Silver

John Sirs

1926 – 2005

John Sirs, Professor of Biophysics at the University of London from 1979-1991, died of a heart attack on 27 April while walking in the Chilterns, an area close to his home and one that he loved. Between 1960 and 1991, he worked at St Mary's Hospital Medical School and was successively lecturer in physics and senior lecturer, reader and professor of biophysics.

Born and bred in the North East of England, John read physics at Durham University and after a short spell in industry, he moved to Cambridge where he became a research student in the small Department of Colloid Science working under the supervision of FJW Roughton. Roughton was a physiologist who had pioneered investigations into the kinetics of the reactions of haemoglobin with oxygen, CO_2, CO and NO. He had discovered carbonic anhydrase and the carbamino compounds of haemoglobin and was one of the first biologists to analyse theoretically and experimentally processes where the overall rate is dependent on both chemical reaction rates and the rates of diffusion of reactants and products to and from the reaction site. John Sirs quickly mastered the physico-chemical techniques of Roughton's laboratory and enjoyed the atmosphere of the small department and also of 1950s Cambridge. After gaining his PhD, he continued his work in Cambridge for a brief post-doctoral period becoming more interested in the physiology of blood gas transport.

In September 1960, John moved to London to take up the position of Lecturer in Physics at St Mary's Hospital Medical School. The main function of the small Physics Department was to provide a first MB course in physics for those 10-15 students who were admitted each year without A-level qualifications in the subject. While teaching was the reason for the department's existence, the head of the department, SG Rowlands, also ran the isotope unit for the medical school, had an active research programme himself, and encouraged his assistants to develop their own research interests. So, as well as teaching elementary physics, John Sirs continued to work on the reactions of gases with the blood and also developed research projects with Rowlands and other members of the department.

An important result of one of these collaborations was first presented as a communication to the Society at the UCL meeting in 1969. This drew attention to the potential importance of Taylor diffusion (the diffusion of a solute between laminae of a fluid flowing at different velocities) in limiting the interpretation of single passage techniques for assessing blood flow and microvascular exchange. The single passage techniques were becoming very popular in the late 1960s, and both the communication and the subsequent paper had real impact. The dispersion of indicators during flow through physical models of complex networks of curved and branching tubes was a topic that John returned to with his research students over the next few years.

Over the next 20 years, John became more and more interested in the physical properties of red cells, particularly the way in which their flexibility influences the flow properties of blood *in vivo*. He developed an original method for assessing red cell flexibility based on centrifugation and published many papers on the rheological properties of blood. He also collaborated with clinicians at St Mary's and elsewhere in London, advising on perfusion systems, blood gas measurements, and investigating altered blood rheology in disease.

In the late 1960s and early 1970s it was thought there was less need for a physics course for medical students, but there was now a requirement to offer a course in statistics. So as the teaching of physics ended, John, assisted by Mike Rampling, developed and ran the statistics course at the medical school until he retired 20 years later. He also became increasingly involved in the teaching of physiology, lecturing on a range of subjects from blood gas transport to membrane potentials.

Former St Mary's students will also remember John Sirs as a very active President of both the Swimming and the Mountaineering Clubs. Not only was he a most enthusiastic coach of the water polo team but, every day that it was possible, he would also find a free half hour for a swim in the medical school swimming pool. As President of the Mountaineering Club he would regularly spend weekends with club members in North Wales, and he led more ambitious expeditions abroad. He remained active both mentally and physically in his retirement. He is sadly missed by his family, former colleagues and friends, and will be remembered with affection by many generations of St Mary's medical students.

C Charles Michel

Encyclopedia of neuroscience

On CD-ROM. 3rd Edition. Edited by George Adelman & Barry Smith. Elsevier, £62.99
ISBN 0444514325

I have spent an interesting few hours using this latest edition of the Encyclopedia of Neuroscience. The CD-ROM format is very accessible for those of us who spend most of our time in front of a computer and the content has been greatly expanded and updated since my old two-volume 1st edition was produced in 1987. It contains 900 entries, of which 18% are new and 60% have been completely revised and updated since the 2nd edition.

The best thing about the encyclopedia is the fact that it is multidisciplinary, with very good cross-linking between articles. There is everything here from cellular neuroscience to the neuropathology of restless legs syndrome and, in passing, I noted a good deal of detail on synaptic physiology, central pattern generators, gap junctions, memory, language, temperature control, pain, schizophrenia, etc, etc. Up till now I have not been able find major absences of information or flaws in the system, which works very well.

All the entries I have seen contain useful references and many of them included classical neuroscience papers. Notes can be added to the various entries by the reader and I found this a useful feature. Diagrams were of variable quality, but many were very good and a lot of them were familiar to me from previous studies. They could be stored in an area called 'light box' for future use and viewed as jpeg or pdf files. Individual entries can be printed out and/or saved as appropriate.

I found this latest edition of the encyclopedia to be a very useful and practical addition to my reference library. At £62.99, it's well worth having on the shelf.

Bill Winlow

Synesthesia: perspectives from cognitive neuroscience

Edited by LC Robertson & N Sagiv
2005, Oxford University Press
ISBN 0-19-516623-X
266 pp, £33.50

Synaesthesia (sic), the production of one type of mental sense impression by the stimulation of a different sense, has been floating around in literature and the consciousness of philosophers, psychologists and others for centuries. The idea that a musical note could summon up the sensation of redness, that different letters should be seen in different colours on the printed page, or that the shape of a chair could induce the taste of coffee, is clearly intriguing. However, until recently the skeptics have been in the ascendancy and Serious Science hasn't taken much interest. As this book demonstrates, that has now changed. The existence of synaesthesia as a real phenomenon is no longer in doubt, and neuroscience has begun to wake up to the fact that here is something interesting and potentially illuminating for it to get to grips with. The well-referenced contributions to this volume deal with general aspects (including varieties of synaesthetic experience), perception and attention, consciousness and cognition, development and learning, and end with a commentary on the implications of synaesthesia for attention, binding and consciousness. There is a good basis here for starting to understand this extraordinary phenomenon, but also a great store of unanswered questions waiting to be explored.

John A Lee

The fatal inheritance

By J Bligh
2004, Athena Press
ISBN 1-84401-336 7
211 pp, £6.99

Like many of the rest of us, physiologist John Bligh is worried about what we're doing to the planet. He feels we have three fatal biological inheritances: a tendency to produce more children than can survive to maturity, self-interest, and aggression in defence of that self-interest. These are exacerbated by our overdeveloped awareness and mental capacities. Bligh fears a future dominated by horrible human population crashes, but hopes that humankind may be able to use its intelligence to prevent this from happening. The book represents his musings on these topics. To my mind, the main difficulty with such general arguments is that 'humankind' does not exist. What exists are groups of individuals, who will indeed act in their own self-interest when it comes to territory, food, water, reproduction and material wealth. The future definitely holds many nasty surprises for humans, and higher population density obviously means more deaths when something happens, as demonstrated recently by the tsunami. Should we fear and hope with Bligh? Or should we shrug our shoulders and head off to the beach while the sun's out? Whatever our rational thoughts, and however smart or well-intentioned we are, in practice most of us do the latter most of the time. I guess this is a case of 'what will be, will be'. Except that it probably won't be as bad as Bligh fears. And if it is that bad, there is probably little we could have realistically done about it.

John A Lee

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

Electrical impedance tomography: methods, history and applications. By DS Holder. Institute of Physics Publishing, £85.00. ISBN 0750309520

Brain and visual perception: the story of a 25-year collaboration. By David H Hubel & Torsten N Wiesel. OUP, £29.95. ISBN 0-19-517618-9

Basic and clinical neurocardiology. By Andrew J Armour & Jeffrey L Ardell. OUP, £50.00. ISBN 0-19-514129-6

PHARMACOGENOMICS

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

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

FUNCTIONAL GENOMICS OF MAMMALIAN NERVOUS SYSTEMS

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

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

BIOSCIENCES FEDERATION EDUCATION COLLOQUIUM

Carisbrooke Hall, Marble Arch, London
12 October 2005

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

EUROPEAN COUNCIL FOR CARDIOVASCULAR RESEARCH

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

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

5th INTERNATIONAL PELVIC FLOOR DYSFUNCTION SOCIETY

Crowne Plaza Panamericano Hotel, Beunos Aires, Argentina
8-11 November 2005

For further information contact the Congress Secretariat at www.ipfds2005.com

Additional Noticeboard listings appear on p. 31

BIOSCIENCES FEDERATION CAREERS CONFERENCES

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

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

THE JOURNAL OF PHYSIOLOGY SYMPOSIUM

Placenta/Endocrine mechanisms of programming
16-20 November 2005

At the 3rd International Congress on the Developmental Origins of Health and Disease, Toronto, Canada (full programme on p. 38).
http://jp.physoc.org

FASEB 2006

Moscone Convention Center, San Francisco, CA, USA
1-5 April 2006
http://www.faseb.org/meetings/eb2006

FAOPS 2006

Federation of Asian and Oceanian Physiological Societies, Seoul, Korea
15-18 October 2006
http://www.faops2006.org

FEDERATION OF EUROPEAN NEUROSCIENCE SOCIETIES

Forum of European Neuroscience in Vienna, Austria
8-12 July 2006
http://www.fens.org

MOLECULAR TECHNIQUES FOR LIFE SCIENCES WORKSHOPS

PCR Theory and Practice
5-9 September 2005
23-27 January 2006

A five day course to introduce participants to this core technique covering the basics to quantitative Real-time PCR. Cost: £740 (Standard); £629 (CPD Accredited)
For further information and application form visit our web site: www.caledonian.ac.uk/mtls or contact: Mrs J Pierotti, MTLS dministrator, Biological and Biomedical Sciences, Glasgow Caledonian University, Cowcaddens Road, Glasgow G4 0BA. Tel: 0141 331 3209; Fax: 0141 331 3208; Email: mtls@gcal.ac.uk

Noticeboard

Notices for the Winter 2005 issue of *Physiology News* should reach the Publications Office by 21 September. Please send contributions to lrimmer@physoc.org.

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

The Physiological Society Meetings

University of Bristol
20-23 July 2005
Joint International Meeting of the Physiological Society and FEPS

University of Oxford
5-7 September 2005 (Mon-Wed)
Focused Meeting on *Ion channels, genes and regulation in smooth muscle*

University College London
19-20 December 2005
Focused Meeting on *The neuroscience of human movement in health and disease*

University College London
July 2006
Physiological Society main Meeting and AGM

Ribeirão Preto, Brazil
27-30 August 2006
Joint International Meeting of the Physiological Society and the Brazilian Physiological Society

Glasgow, Scotland
8-12 July 2007
Joint Meeting of the Physiological Society, Biochemical Society and British Pharmacological Society

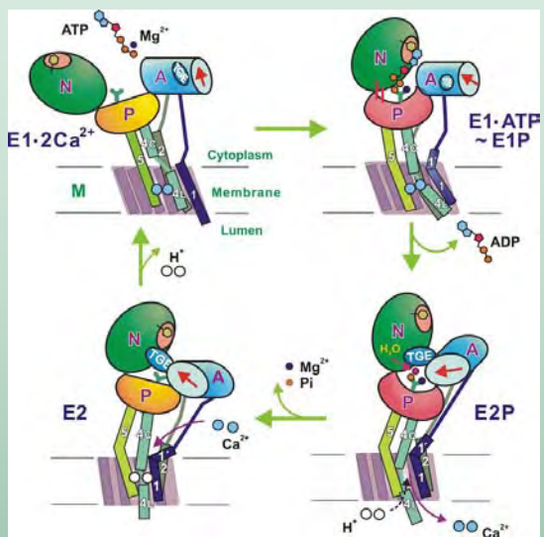
Bratislava, Slovakia
10-14 September 2007
Joint Meeting of the Physiological Society, the Slovakian Physiological Society and FEPS

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

General enquiries
meetings@physoc.org

11th International ATPase Conference
and
59th Annual Meeting and Symposium of the Society of General Physiologists
September 6-11, 2005

Marine Biological Laboratory, Woods Hole, Massachusetts



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Na,K-ATPase & Related Cation Pumps: Structures, Mechanisms & Diseases

Organized by David Gadsby, Jack Kaplan, & Jerry Lingrel

Atomic structure of cation pumps
Paul De Weer, Chair
Yuji Sugita
Jesper Møller
Steven Karlish

Cation binding sites
Jean-Daniel Horisberger, Chair
Peter Jørgensen
José Argüello
Hans-Jürgen Apell
Pablo Artigas

Ion transport mechanisms
Luis Beaugé, Chair
Giuseppe Inesi
Jens Peter Andersen

Cation pump subunit interactions
Kazuya Taniguchi, Chair
Ernst Bamberg
Jack Kaplan
Ayyappan Rajasekaran

Inherited dysfunction of cation pumps
Carolyn Slayman, Chair
Kathy Sweadner
Rhoda Blostein
Amy Moseley
Svetlana Lutsenko

Late-Breaking Science
Speakers to be determined

Regulation of cation pumps
FXYD proteins
Michael Caplan, Chair
Kathi Geering
Flemming Cornelius
Haim Garty

Phospholamban and sarcolipin
Don Bers, Chair
David MacLennan
David Thomas

Specific P-type ATPase inhibitors
Robert Farley, Chair
Jan Joep De Pont
George Sachs

Receptor-mediated regulation
Carlos Pedemonte, Chair
Alejandro Bertorello

Physiological roles of cation pumps
Mordecai Blaustein, Chair
Jerry Lingrel
Gary Shull
J. Iasha Sznajder

For further information, contact David Gadsby (gadsby@rockefeller.edu)

BIOSCIENCES FEDERATION

BIOSCIENCES FEDERATION EDUCATION COLLOQUIUM 2005

Student Employability: Whose Job Is It?

Taking responsibility for training bioscientists

Wednesday 12 October, Carisbrooke Hall, Victory Services Club, Marble Arch
9.15 am - 4.00 pm

What and who makes a bioscience student employable?

This workshop invites school and university teachers, employers, educational and careers professionals to discuss how schools, universities and industry can enhance student employability. It will focus on key questions and culminate in a set of published recommendations.

Talks include:

- What influences science choice at secondary level?
- From QCA to specification
- How do degree courses measure up?
- Employer expectations and requirements

For more details and to register for the meeting go to: www.bsf.ac.uk/edu