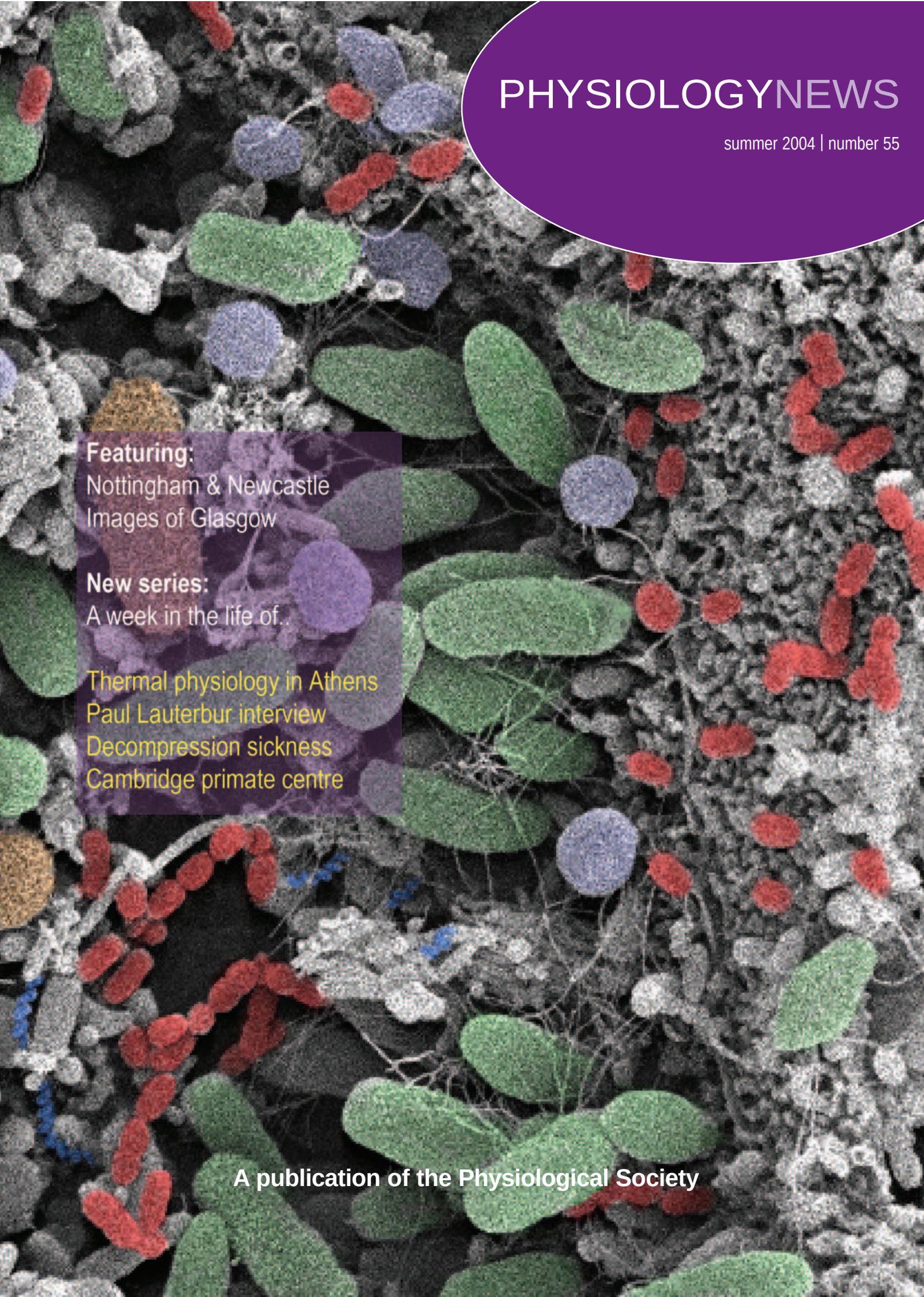


PHYSIOLOGYNEWS

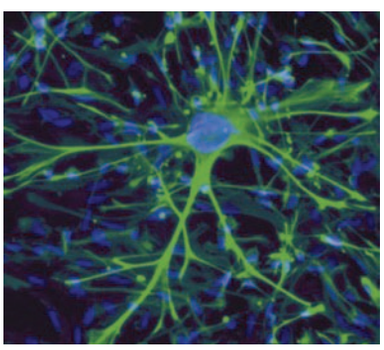
summer 2004 | number 55

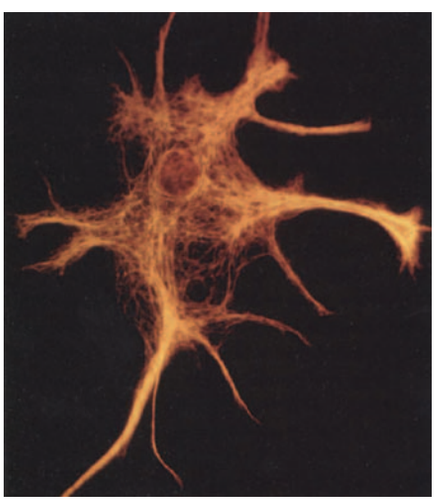
Featuring:
Nottingham & Newcastle
Images of Glasgow

New series:
A week in the life of..

Thermal physiology in Athens
Paul Lauterbur interview
Decompression sickness
Cambridge primate centre

A publication of the Physiological Society





Images of physiology

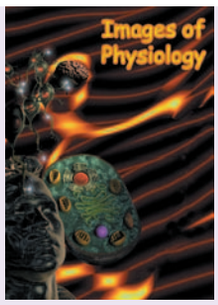
Thelma Lovick takes a sideways look at neuroscience

Have you ever noticed how fashions change in physiology? How the most unlikely findings, once relegated to the 'interesting' phenomena file, suddenly become the latest thing? Or how significant progress, sometimes made in the late 19th or early 20th century, lies apparently dormant for decades?

Such bits of information languish in dark recesses of the collective memory, using up space that could more usefully(?) be dedicated to the really cutting edge stuff. But then the scientific climate changes and, suddenly, yesterday's worthy-but-dull fact gets re-examined, dusted off and catapulted to superstardom. One such candidate for superstar status has to be the humble astrocyte.

Golgi and Cajal lit a slow-burning fuse

Where did it all start? Well, as with so much in the brain, you will find that Cajal and Golgi had been there, stained it, named it and drawn a pretty accurate picture - some 100 years or so previously. But the fuse they lit burned very slowly, at least in the physiological consciousness. Astrocytes smouldered for a few decades…there were lots of them in the brain but they seemed very much back seat players. Outnumbering neurones by about 10 to one in man, they provided a supportive scaffold for neurones and generally kept the extracellular environment tidy by mopping up excess potassium…and that seemed to be it. Because the real players in the brain were the neurones.



Emancipation of astrocytes

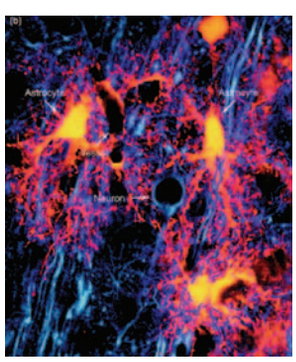
Then in the mid '80s, their time had come. Between 1985 and 1990 there was a 500-fold increase in the annual rate of publications on astrocytes (data from ISI Web of Science). These days you can hardly open a neuroscience journal without an astrocyte falling out. And they are so photogenic…quite beautiful and, thanks to modern image enhancement software, they now come in a huge range of attractive colours.

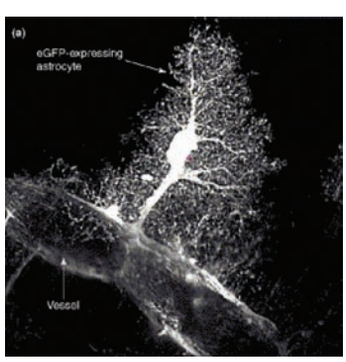
Glial power

Now, astrocytes are recognised as crucial participants in almost all of the integrated functions of the nervous system. They clean, they feed, they nurture, they repair. And who do they do it for? It's for those macho neurones. Behind every successful/powerful neurone is a fleet of astrocytes whose contribution has, until recently, gone largely unrecognised. Are you surprised? You shouldn't be, it's just a case of neuroscience imitating life.

Thelma Lovick

Send in your contributions for 'Images of physiology'. A £50 prize awaits the best image received for each issue of *Physiology News*.





Far left, from the top:
Cajal (left) and Golgi
Astrocytes as seen by Cajal
Cambrex online catalogue (www.cambrex.com)
sfn.org brain briefings, December, 2000 (Vladimir Purpura)
Nedergaard et al (2003). *TINS*, 26, 523-530
Left:
Nedergaard et al (2003). *TINS*, 26, 523-530

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

Contributions and Queries

Executive Editor
Linda Rimmer
The Physiological Society
Publications Office
Building 4A, The Michael Young Centre
Purbeck Road
Cambridge CB2 2HP

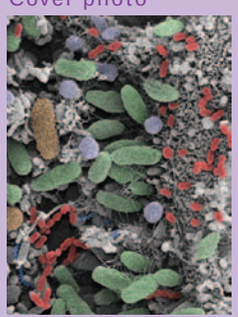
Tel: +44 (0)1223 400180
Fax: +44 (0)1223 246858
Email: lrimmer@physoc.org
The Society web server: http://www.physoc.org

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



The scanning electron microscope image was generated by the Biomedical EM Unit of the University of Newcastle-upon-Tyne and shows bovine rumen epithelium with adherent microflora. This work was funded by a grant from Pfizer Global Research to C. Graham and N.L. Simmons (School of Cell and Molecular Biosciences)

PHYSIOLOGYNEWS

Contents

Editorial 3

Newcastle Meeting *Barry Hirst* 4
Nottingham Meeting *Paul Greenhaff, Michael Rennie* 4
Images of Glasgow 6, 38, 40

Features

The Athens Olympics: some lessons in thermal physiology *Ron Maughan* 5
That was the week that was ... *Alan North* 7
Halt on Cambridge primate centre *Nancy Rothwell* 11
From magnetic moments to medical imaging *Austin Elliott* 12
Can a single bout of exercise prevent decompression sickness? *Ulrik Wisløff, Russell S Richardson, Zeljko Dujic, Alf O Brubakk* 16
Understanding skeletal muscle hypertrophy: integration of cell signalling *Douglas Bolster, Neil Kubica, Stephen Crozier, David Williamson, Peter Farrell, Scot Kimball, Leonard Jefferson* 18
Bidirectional synaptic plasticity and motor learning in the cerebellum *Francis Crépel, Armelle Rancillac* 20
The large conductance calcium-activated potassium channel (BK_{Ca}) and the $ß_2$ adrenergic receptor (AR): a direct link to uterine relaxation *Boonsri Chanrachakul, Fiona Broughton Pipkin, Raheela N Khan* 22
Imaging the activity of single calcium channels: 'optical patch-clamp recording' *Angelo Demuro, Ian Parker* 24
Brain waves plainly speaking *Yacov Fischer* 27
Getting insight into the work of tendons *Oksana Kostyuk, Robert Brown* 28
Vasopressin may limit its own secretion with the help of pituicytes *Lia Rosso, Brigitta Peteri-Brunbäck, Jean-Marc Mienville* 30
Qualia and private languages *Denis Noble* 32

International News

Clinical physiology in Warsaw *Bohdan Lewartowski, Andrzej Beresewicz* 34
Why British physiologists should be part of the European Space Programme *Michael J Rennie* 35

Council activities 10
The Journal of Physiology 37

Affiliate News

UK Grad courses *Laura Blackburn* 38

Letters to the Editor 39

Society News

Voices of the Future 2004 *Emily Ferenczi, Andrew Murton* 43
Deputy Executive Secretary on winning team *Maggie Leggett* 44
Biosciences Federation *Maggie Leggett* 44
Pfizer Prizes 45

Unbelievable! 46

Obituaries

Gerald A Kerkut *Robert J Walker* 47
John Atherton Young *Maynard Case* 49
Graham Francis Baker *Malcolm Segal, Richard Naftalin* 49
Nachman Ambache *Desmond Greaves* 50
Hannelore Pawelzik *Alex Thomson* 50

Book Reviews 51
Noticeboard 52

PHYSIOLOGYNEWS

Action points

Grants

Grant schemes have changed. For full information on Members' and Affiliates' Grants, Pfizer In Vivo Physiology Grants, Intercalated BSs Bursaries, Network Interaction Grants, Non-Society Symposia Grants, Postgraduate Support Fund information and the Vacation Studentship Scheme please visit:
http://www.physoc.org/grants

Membership applications

Applications for Full and Affiliate Membership are received throughout the year and have no deadlines. A decision is normally made within 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

Physiology News

Deadlines

Letters and articles and all other contributions for inclusion in the Autumn 2004 issue, No. 56, should reach the Publications Office (lrimmer@physoc.org) by 7 June, 2004. The copy date for the Winter 2004 issue, No. 57, is 20 September. Late copy can be included if space permits.

Suggestions for articles

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

Physiology News Online

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

In this issue

Welcome to the Summer issue.

One of the things we like to bring out in *Physiology News* is the great variety of ways one can practise experimental physiology, and the different places one can carry it out. This time we have pieces relating to physiology in Poland (p. 34), in space (p. 35), under the sea (p. 16), in the searing heat (p. 5), in the operating theatre and anaesthetic recovery room room (p. 39) and even in Birmingham (p. 40). We have 20 pages of scientific articles and another 9 pages of features.

Talking of features, in this issue we launch a new series: 'A week in the life of ...' Each issue a Society member will tell us about his or her working week - we kick off with Society President Alan North. In future issues we hope to use this series to bring home the full range of what Members do with their working time – in Britain and abroad, in universities and other research environments, and in other kinds of jobs. A training in physiology can take people into all sorts of occupations, as we hope you will see as the series develops.

We are also committed to bringing you news on issues relevant to physiologists. Apart from the regular Society news, Nancy Rothwell discusses the halt on the Cambridge Primate Centre (p. 11), while young scientists Emily Ferenczi and Andrew Murton report on meeting the parliamentarians, including Secretary of State for Education Charles Clarke (p. 43). Finally, several writers in this issue are worried about a traditional role of university physiologists, namely teaching medical students (see pp. 23, 40-41 and 46). Is this 'service' teaching undervalued? Or should we still be doing it at all?
We are keen to hear what you, the Members, think. Let's keep emailing and make the *Physiology News* letters column a real forum for discussion on this and any other issue you feel strongly about.

Austin Elliott

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 between the contributor and the commissioning editor. Submission of articles
Authors should submit text in the form of a disk or emailed Word document, to reduce the risk of introduction of errors during re-typing.

Illustrations and authors' photographs

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

References

Authors are requested to keep the number of references to a minimum – preferably no more than two or three. Please cite all references in the style of *The Journal of Physiology* (see *Instructions to Authors 2004* on the Society's website:

http://www.physoc.org).

Submission deadlines

Please contact the Executive Editor in the Publications Office (see Contents page for details) for submission deadlines. Submissions may be deferred to a subsequent issue, depending on available space. Short news items are encouraged and can usually be included as late copy.

Time to communicate?

Most of us in science agree that better science education of the wider public is a good thing. And the contemporary view, coming from *inter alia* the top of learned societies and research councils, is that this requires much greater 'public engagement' by the scientific community. But how, exactly, is this going to happen? Should learned societies, like the Physiological Society, do more? If so, how? Should individual universities do more? Should individual scientists, like Society Members and readers of this magazine, do more? How?

Let's start with the easy things. There is no doubt that more science in the public eye brings benefits, particularly in terms of getting children interested in studying science. As a child in the late 60s – and like, I suspect, many 40-something scientists - I was totally gripped by watching, and reading about, the Apollo missions and moon landings – perhaps one of the greatest examples of an event, wholly based on science and engineering, which captured global public imagination.

Although the Human Genome Project and the discovery of human stem cells are undoubtedly epochal scientific events, they have yet to find their public 'hook' – their equivalent of putting a man in space, or on the moon.

The importance of using opportunities like those presented by 'experiments in orbit' to get young people turned on to biological sciences is something that Mike Rennie emphasises in his article about the European Space Programme on p. 35 of this issue. One suspects that something happening now, like the Beagle 2 project, speaks to the public far more than the airy promises of future cures from genome-based research. There is also the danger that too much talking up the future causes cynicism when delivery is slow; gene therapy for cystic fibrosis, anyone?

Still on capturing the interest of future young scientists, it is clear that, for secondary school children taking science subjects, television science programmes in particular play an important role in getting them interested in studying biological sciences at university level.

Anyone who has interviewed prospective UK physiology undergraduates over the last decade will have heard television series and televised lectures given by people like Colin Blakemore, Susan Greenfield and Nancy Rothwell repeatedly mentioned as one of the things that inspired them to apply to do a physiology, or other bioscience, degree. In this context it is worrying to hear that the Royal Institution Christmas Lecture Series is apparently under threat.

So what can the learned societies do? First, they are not idle now. The Physiological Society organises an annual workshop for the public (at the British Association Festival of Science), produces booklets for schools, helps support a database of scientists willing to talk in schools, and organises several workshops a year for schoolchildren and one for teachers. It has also recently started issuing press releases. But it is fair to say that it, and the other similar societies, could probably do more.

At the individual level, what can Members do? Many universities now run schemes for staff to go to local schools and discuss science and scientific issues with children – public engagement at the grass roots. However, this inevitably takes time and effort. Some research scientists describe their work for publications aimed at a general audience, or at specific target groups such as 6th form science students. Sadly, any exposure raises inevitable issues regarding animal rights protests for those who 'go public'. But – and, I suspect, more universally – there is also the problem that writing 'popular' articles takes time that could otherwise be spent cranking out grant proposals or papers. This brings me to a final critical point. All the upbeat talk about scientists needing to engage more with the public is great – but possibly over-optimistic. Let me pose a rhetorical question. Would a major UK research university in 2004 rather an individual staff member were writing a grant proprosal, a research paper, or a popular science book directed at a non-specialist audience? It is pretty clear the answer would be the first preferred over the second, and both of these heavily preferred over the third – although 'all three' might be acceptable. Within the research community, the people who have been most prominent in communicating science to a wider audience have tended to be highly successful researchers who have somehow found the extra time to add communication to their other activities. However, these people are clearly special in many ways, including their ability to deal with workloads way beyond the norm. One might suspect that there must be other people – ordinary mortals? - within the science base who could contribute usefully to science communication, if they could find the space and time.

Perhaps the answer is to fund more academic posts specifically in Science Communication, or Public Understanding of Science. Perhaps universities could second lecturing staff from their 'normal' activities to 'public science communication duties' for part of their time. Research Councils and other funding agencies could offer more grants targeted at efforts in science communication, or fellowships to enable staff time to be purchased for this kind of work. The danger is that, without a continuing commitment to imaginative solutions of this kind – and without investment of real money to support them – all the good intentions in the world are not going to deliver more public engagement from ever-harder-pressed science researchers and teachers.

Austin Elliott

Nottingham Meeting

Responsiveness of muscle, bone and connective tissue to physical activity: genetic and molecular integration

A Physiological Society Focused Meeting of the Human Physiology Special Interest Group will take place at Nottingham University Medical School in Derby on 12-13 July, 2004.

The application of modern techniques of physiological, pathophysiological and post genomic technology is providing us with unforeseen knowledge concerning the way in which the musculoskeletal mass, which comprises 80% of our lean tissue mass, maintains itself and adapts to differing degrees of physical activity and changing environments. Some remarkable physiological phenomena have been discovered, e.g. the marked anabolic response of bone to vibration, the linking of changes in muscle myofilament turnover with the turnover of extracellular matrix, the marked response of tendon to exercise, and the existence of genetic traits which make human beings good or poor responders to exercise.

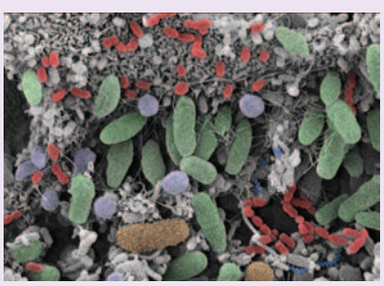
This Focused Meeting of the Society will allow the latest physiological findings to be set in a context of transcriptional and translational control of the tissues of the musculoskeletal system some of which, like bone and tendon, were hitherto thought only to respond weakly and slowly. Furthermore, the programme will include oral communication and poster presentations by attendees.

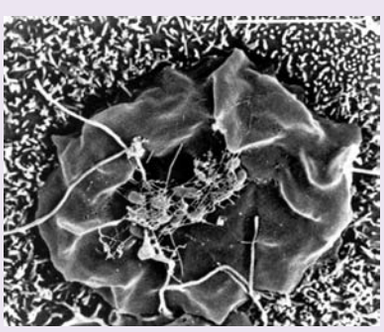
The Meeting will take place at Nottingham University Medical School in Derby, which has brand new state of the art audio-visual facilities and lecture theatres. Accommodation will be within easy walking distance of the meeting, a Society dinner will take place at the Meeting and plans are in place to run a social programme in tandem with the Meeting. Attendance will be limited to 100 delegates on a first come first served basis. Programme and registration details will be available at: http://meetings.physoc.org/

Paul Greenhaff
Michael Rennie
University of Nottingham

Newcastle Meeting

Epithelial-bacterial pathogen interactions





A Physiological Society Focused Meeting will take place at the University of Newcastle-upon-Tyne on 22-23 July, 2004.

This highly Focused Meeting will consist of two related symposia, discussing the interactions of human pathogens with respiratory and intestinal epithelia. The aim will be to highlight recent developments in our understanding of how bacteria interact and modulate the physiological function of these epithelial barriers, at the molecular, cellular and whole tissue level.

Speakers at the first of the two symposia (Epithelial-bacterial pathogen interactions: new insights into host response to acute and chronic lung infections. Who is talking to who?) will include Brad Britigan, Gerd Doering, Ed Galyov, Peter Greenberg and Florian Lang. This symposium is organised by Mike Gray and Phillip Aldridge.

Gadi Frankel, Martin Kagnoff, Brendan Kenny, Nicholas Mantis, Andre Ouellette and Andrea Varro will speak at the second symposium (Epithelial-bacterial pathogen interactions: subversion of physiological processes in the gut), organised by Barry Hirst and Anjam Khan.

Free communications and posters will be presented during the Meeting following Physiological Society guidelines. Registration, which is necessary to attend, is free to Society Members and members of the University of Newcastle-upon-Tyne and will be available at: http://meetings.physoc.org/

Further information is also available from the University of Newcastle-upon-Tyne website at: http://www.ncl.ac.uk/camb/research/EBPI/index.htm

Barry Hirst
University of Newcastle-upon-Tyne

The Athens Olympics: some lessons in thermal physiology

Ron Maughan continues our series of articles on exercise physiology in the run up to the summer Games

Every few years a major sporting event takes place in an environment that poses special challenges to the participants. It may be altitude, cold or air pollution but, more often, it is heat that causes the biggest problems. Over the years, there have been many examples of spectacular collapses in marathon races, including the examples of Dorando Pietri, who collapsed on the track close to the finish of the 1908 Olympic Marathon in London, Jim Peters, who fell to the track in the Empire Games Marathon in Vancouver in 1954, and many other less high profile problems. These problems are seldom seen when competition takes place in cool environments – although athletes still experience extreme fatigue – and they are most often seen in events lasting an hour or more.

In my days as a physiology student, there was an ongoing debate as to whether the limitation to exercise performance lay in the cardiovascular system or in the active muscles. The re-introduction of the needle biopsy technique for sampling skeletal muscle provided compelling evidence that fatigue in prolonged exercise – at least in cycling, but less convincingly so in running – was a consequence of depletion of the muscle glycogen store. When carbohydrate is not available to the muscles at a rate sufficient to allow the rate of ATP resynthesis to match the rate of hydrolysis, then the energy demand – the speed of running or cycling – must drop to a point where it can be met by fat oxidation. Even in trained athletes, the maximum rate of ATP resynthesis that can be achieved by fat oxidation is only about 50% of that from carbohydrate oxidation.

However, several lines of evidence now suggest that this is irrelevant when exercise takes place in a warm environment. Exercise capacity – measured as the time for which a fixed speed can be sustained – is reduced progressively as the temperature increases above an optimum level,

Fluid intake is important in maintaining cardiovascular function and thermal homeostasis, and athletes will look at optimising their hydration strategies

which may be about 5-15ºC. At the point of fatigue in exercise in the heat, the muscle glycogen content remains high, so substrate availability seems not to be limiting. There is also compelling evidence that raising body temperature prior to exercise can impair performance, while pre-exercise cooling can improve performance. These manipulations have little or no effect on the pattern of substrate use in skeletal muscle.

In 1993, Bodil Nielsen wrote in *The Journal of Physiology* that 'Physical endurance in hot, dry environments appears to be limited by attainment of a critical level of core temperature, perhaps due to temperature reducing motivation.' She proposed that attainment of a critical core temperature would inevitably result in fatigue, as a protective mechanism against thermal injury. At the time, objections to Nielsen's Critical Core Temperature Hypothesis were raised, in particular the failure to provide a plausible biological mechanism for this phenomenon. There was also no evidence of a specific core temperature at which fatigue ensued. However, the typical measure of core temperature in exercise physiology studies is rectal temperature, and no-one would believe that the rectum is the site of fatigue. Since then, however, animal studies have provided evidence that there is a critical level of brain temperature beyond which animals will not continue to exercise voluntarily. The Copenhagen group have applied this to man, providing compelling evidence for a thermal limitation to performance: cerebral heat exchange was measured in exercising subjects by continuous monitoring of aortic and internal jugular vein temperatures during exercise. They found that brain temperature is higher than core (arterial) temperature. At high ambient temperature, heat loss is reduced, so brain temperature rises much faster.

Over the years, there have been many examples of spectacular collapses in marathon races

They have also shown an altered EEG pattern in hyperthermia consistent with changes in motor neuron activation thresholds and increased perception of fatigue. In a further study, they showed reduced force generating capacity in individual muscle groups when core temperature was high. Further support for a link between a hot brain and fatigue comes from an abstract presented at last year's annual meeting of the American College of Sports Medicine. Subjects were exposed to passive heating by a water perfused suit, and the MVC of the knee extensor muscles was measured. Muscle activation was assessed by the twitch interpolation technique. Activation decreased from 80±10% at baseline to 65±11% when rectal temperature reached 38.5°C.

The rise in core temperature during exercise in the heat is limited by evaporative heat loss, but this has two consequences. Fluid loss as a consequence of sweating impairs cardiovascular function, and cardiac output falls. Maintenance of a high rate of evaporative heat loss requires a high skin temperature to maintain the vapour pressure gradient that drives evaporative heat loss. To maintain a high skin temperature, however, requires a high skin blood flow, and a falling cardiac output does not permit this.

Various strategies are available to the athlete to help cope with the conditions anticipated in Athens. Prior heat acclimation improves sweating responses and there is some evidence that it also lowers pre-exercise core temperature. Fluid intake is important in maintaining cardiovascular function and thermal homeostasis, and athletes will look at optimising their hydration strategies. Pre-exercise cooling, and cooling between successive rounds of competition, will be employed by some. How effective these strategies are will have some bearing on who wins the gold medal in some events.

Although we now understand much more about the thermal limitations to exercise performance than we did a few years ago, there are still important lessons from the older literature. In an excellent textbook published in 1919, Bainbridge (he of reflex fame) was able to write that 'It has long been recognised that the main seat of fatigue after muscular exercise is the central nervous system. Mosso long ago stated that 'nervous fatigue is the preponderating phenomenon and muscular fatigue is also at bottom an exhaustion of the nervous system.There appear, however, to be two types of fatigue, one arising entirely within the central nervous system, the other in which fatigue of the muscles themselves is superadded to that of the nervous system'. That sounds like a pretty good description of the current state of thinking.

Ron Maughan
School of Sport and Exercise Sciences, Loughborough University, Loughborough, UK

In the next issue Mike Gleeson writes on training and competition stress: effects on immune function and health and Henning Wackerhage and Phil Atherton explain adaptations to marathon training

Images of Glasgow

Clockwise from top, left:
A man and his toys - David Eisner, complete with laptop, PDA, mobile phone AND camera!; This imposing biological exhibit stands guard outside the Hunterian Museum (we don't know if he supports Celtic or Rangers); The Hunterian Museum and other nearby Glasgow University buildings give the Meeting site a very Victorian Gothic feel; The hot seat - this chair contains a black stone on which Glasgow University students were required to sit for their Oral Examinations. This was the practise from the beginning of Glasgow University until the mid-19th century. Note the hourglass, presumably for timing the examination; Godfrey Smith with symposium speakers Jon Lederer (left) and Guy Salama.

(Photographs by Austin Elliott)
See p. 38 for Glasgow: art and culture

That was the week that was...

No week is typical for Alan North, so he chose this one, when magazine Editor Austin Elliott finally persuaded him to move the piece up his mind's agenda and onto paper...

Sunday

This day begins in the lounge at Heathrow airport, reading my email. I am returning from a very brief meeting in Minneapolis, advising a small company starting up in the pain area. I admire the entrepreneurs who will turn science into medicines, in this or any other area, but after another British Airways night I am wondering how long I can keep up this particular kind of long distance support. Among the email correspondence: Maynard Case has some pieces relating to my impending move to Manchester; David Brown is giving information on the up-coming St Petersburg meeting on membrane transport – and also responding to my suggestion to hold a symposium to honour the recently deceased autonomic physiologist Vladimir Skok – and, no surprise, a request to review a manuscript from one of the Senior Editors of *The Journal of Physiology.*

On the plane up to Manchester, I work some more on the further drafting of a paper destined for *J Gen Physiol* that deals with the channel vs pore features of the $P2X_7$ receptor. Like many of my recent papers, this one was easily conceived, but has been too many months in gestation. It is getting close, though some aspects need to be played down a bit and a couple of figures re-jigged. I feel that the paper needs a quantitative model to illustrate the conclusions; I started on it some months ago but am doubtful now that I will ever find the time to finish it.

I currently serve as Chair of the MRC Cross Board panel and there is a briefing meeting scheduled for Monday at 3.30 pm. But when I get home to Sheffield I realise that the final set of papers (the referees' comments) arrived at my office only on the Friday, so I have to go into my office at the University to pick them up. Not too bad, the pile of papers is only three inches high, and luckily it is also on

Figure 1. Alan North, current President of the Physiological Society

CD. Sadly, I now realise that my mobile phone, which I had noticed missing at Manchester airport on Thursday, was not plugged into the charger in my office – the one place that I thought I was most likely to find it. I had felt rather naked without it in the US – funny how these recent technologies so quickly become essentials.

Monday

I am in the office soon after eight, which is about usual, having dropped off my 11 year old son at his school close to the University. Adrian prefers the croissants that are available there to the breakfast that I might prepare! There is not a lot of activity in the laboratory at that time of day, but my assistant Jessica Hinchliffe soon arrives. Even before she has taken off her coat I beseech her to help retrieve/cancel/replace my phone! She is unflappable – it will be done. A new meeting has appeared in the calendar for 9.00 am. This is with a colleague (Kei Cho), with whom I am organising a substantive collaboration with the Brain Research Centre in Seoul. It is a joint venture with neuroscientists in Bristol and Sheffield, and needs some urgent discussion in the light of my forthcoming transfer to the University of Manchester. And probably, I discover, it will necessitate an early trip to Korea.

Hye-Youn, a research assistant carrying out RT-PCR on lung ion channels, tells me that our stored human lung macrophage RNA has partially degraded after some months in the freezer. This project forms part of a collaboration with AstraZeneca and is run by a senior postdoctoral colleague Amanda Mackenzie: we get together to re-prioritize our study of some remaining channels. The choice is made more problematic by the realisation that the departmental fluorescence-activated cell sorter is no longer available (the technician recently quit), making it difficult to isolate a further supply of cells. It is the modern way of science, which requires a long term management effort to coordinate the participation of surgeons, other academic colleagues, FACS technicians, and electrophysiologists. Then suddenly one link in the chain breaks. A different form of physiology from my early days – take an animal and start the experiment in the morning, and continue until the cells or the preparation faded in the evening (or early the next morning!).

Jessica tells me about the missing phone -- the bad news is that it is not in any of the obvious places where I might have left it, but the good news is that nobody has put thousands of pounds worth of calls on it over the weekend. There would normally have been a few phone calls to make on my journey down to London, although unlike most of my fellow travellers I have a distinct aversion to discussing any kind of business in railway carriages. So I find some fortuitous peace in that regard, and have the chance for a final read through the referees' reports for the 44 MRC grants – they are easy to go through on a lap-top. The meeting at 3.30 pm is with the MRC staff responsible for the grant

applications. It gives us the opportunity to highlight any particular areas of concern, so that we can alert primary reviewers if necessary in the two days prior to the review meeting itself.

That evening is a pleasant event in which I join about 20 others for dinner at a small Italian restaurant in the Lambeth area – they are the Council of the Physiological Society. Some say, indeed some Council members say, that the events are a boondoggle, and an unnecessary expense. In fact, I spend the meeting in conversation with Giovanni Mann and Maggie Leggett discussing possible new ways to support younger physiologists, and particularly how to involve physiology undergraduates and PhD students in school visits. The food and wine do 'enable' such discussions, and I feel that they are a useful adjunct to the formal meetings of Council.

Tuesday

The London hotel is not too luxurious and some Council members can find no seat for breakfast; those of us who do, continue much of the previous evening's conversations. It is a 20 minute walk over to Guy's for the meeting itself and its 9.30 am start. One of the most significant agenda items is the provision of substantial funds to rectify a pension shortfall for some of the Society's staff. The Executive had previously considered this at length, and of course taken professional advice. Nonetheless, it is good to see significant Council discussion with many members taking part, which ultimately led to a revised decision which all considered fair.

There are other key items: a bid to host the 2013 International Union of Physiological Sciences congress must be prepared by the end of September. And, talk about forward planning, a small budget was approved for lobbying efforts to place physiological sciences in the funding picture with respect to the Aurora manned mission to Mars scheduled for 2031. Whereas Meetings Secretary Bridget Lumb apologised that she would not be holding her post in 2013, there was no such humility on the part of Mike Rennie with respect to the Mars mission in 2031!

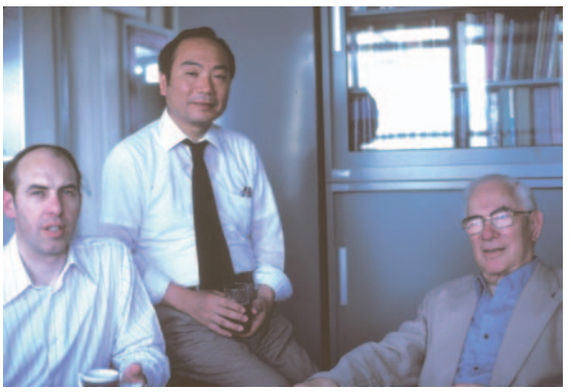


Figure 2. Tribute to mentors. Gordon Lees, Syogoro Nishi, Hans Kosterlitz (left to right). Syogoro Nishi is an honorary member of The Physiological Society, Gordon Lees an honorary member of the British Pharmacological Society, and the late Hans Kosterlitz was an honorary member of both societies.

I bring the meeting to a close at 11.45 am and, after a quick sandwich with Council members, I take a cab over to the London offices of Nature Publishing Group. They publish the *British Journal of Pharmacology* (BJP), of which I am currently Editor-in-Chief. At the meeting are two of our Senior Editors, the journal manager, Nature Publishing Group staff and an outside consultant. On the agenda there is a new meeting that is being planned to promote the BJP, very much modelled on *The Journal of Physiology* symposia that have been held around the world in the past few years. This time the topic is 'Pharmacology of the Lower Urinary Tract', planned for December 2005 in association with a meeting of the Scientific Branch of the American Urological Association (SBUR). These things need a good head start – in this case the arrangements are potentially complex, involving NPG, BJP and the SBUR. We discuss the outline of a joint contract, and the urgent need for a provisional business plan to get the project off the ground.

Back in Sheffield at 5.00 pm I have a meeting scheduled with Mark Dunne. Mark was, until recently, the Society's Meetings Secretary. He is head of the Division of Physiology, Pharmacology and Toxicology in Manchester, and this meeting has to do with space and facilities in Manchester when I move there in July. Thanks to Midland Mainline I arrive 30 min late for the meeting – the journey is not atypical (service first delayed and then cancelled at Luton and the entire train contents disgorged onto an adjacent train). On the other hand, one journey from London to Sheffield last year that should have been a 2 h 10 min direct service involved me travelling on four different trains and arriving 3 h late, so all things are relative. The loss of my phone prevented me from telling Mark of my delay. But the train journey allowed me to make a start on this article...

After some time spent poring over future floor plans I leave the laboratory around 7.00 pm. This was good timing to pick up my son from his football practice, and get home to watch the game between Arsenal and Celta Vigo with him. And, as the day was Shrove Tuesday, the half-time interval allows me to cook the traditional pancake fare. In this part of the world these are thin crêpes served slightly crisped with sugar and lemon juice: they are most often eaten for breakfast, but evening serves equally well!

Wednesday

A day in the laboratory, with few appointments. Still a lot of reading to do in preparation for the panel meeting at the MRC tomorrow. The day starts with a session with Jessica, which brings the urgent realisation that the date of the next meeting that I had proudly announced to the Physiological Society Council yesterday was the wrong one. I am a slow learner, but now I have at last figured out that my calendar is best left entirely to

somebody else. Jessica calls David Sewell and we send out an immediate correction and abject apology.

A third year undergraduate student comes to see me about his library project on $P2X_3$ receptors and pain. I was most impressed at the list of a dozen or so papers that he had prepared for discussion, including a very recent review by R A North in *The Journal of Physiology* entitled '$P2X_3$ receptors and pain'. Seems like one student on his way to a First Class degree!

At 12.30 pm the informal 'journal club' takes place; this is a 10-15 min whiteboard presentation by someone in the lab of a recent paper. The event has been running daily at 12.30 pm in my laboratory for about 25 years, with many stops and starts, and survives because of its essential informality (which is another way of saying that you don't come to listen if you have something more important to do, like an experiment, and you don't come to present if you are lazy, fearful or uninspired). The presenters rotate through all laboratory members – professors to PhD students; today it is one of my own graduate students.

Half an hour with another member of staff dissecting and discussing a paper prepared for submission that I had read on the last US trip. Half an hour spent writing a letter of reference for an appointee to an overseas professorship. Two hours reviewing overdue manuscripts for *The Journal of Physiology* and other journals.

And then home around 4.00 pm because that's where the MRC grants are (the 12 inch pile) for tomorrow's meeting. I put another 3 h into them before it's time to fix dinner.
My wife Annmarie Surprenant (who is also a professor in the Institute of Molecular Physiology at the University of Sheffield) has spent the latter part of the day visiting AstraZeneca, with whom she holds a research collaboration. She is enthused about the possibility of perhaps, at long last, being able to publish some of the work that has been carried out with their compounds; in fact they have turned out to be good tools with which to probe physiological function, and the scientific community needs them in the public domain. She was less enthusiastic about the earlier part of the day, which saw her taking an examination set by the Home Office. Nonetheless, she had some entertaining stories –such as one of her biochemical colleagues who had asserted in response to one question that the typical weight of an adult laboratory rat was 1 kg.

Thursday

Today is a 6.00 am start, and I am into London soon after 9.00 am. The two hour train ride allows the final preparation for the Cross Board meeting. The MRC Council room is filled today, no apologies received. The 20 members of the Board are drawn from all areas of medical science, ranging from clinical trials and public health to protein structure. They have a tough task, reviewing grants that are sometimes distant to their expertise, but aided with several expert referees' reports. Some grants reach early consensus in minutes, other require discussion for an hour. The meeting is business-like and forthright, and I am once more impressed by the care and fairness with which these Board members contribute to the peer review process. This is the penultimate meeting of the Cross Board Group, which is destined to be replaced in the summer of 2004 in the new portfolio of MRC grants recently announced. The meeting finishes at 4.00 pm after a final reflective view of the outcomes, aided in this modern age by a projected display of a spread-sheet on a large screen. I like this system because it is fully transparent, and gives all the Board members the opportunity to re-open discussion, or to revise or refine their assessments of the grants considered for support. Most importantly, it allows the entire group explicitly to take responsibility for the collective decision.

The 4.00 pm finish allows me time to visit Waterstone's down by University College before meeting my 19 year old son Chris. I am looking for a book by Donald Kennedy, a scion of American academic life who is now Editor-in-Chief of *Science*. Chris is a student at the Guildhall School of Music, specialising in Composition. We find a nice restaurant on Charlotte Street and after another beer or two I finish up running for the 9.25 pm train from St Pancras. This means home around midnight.

Friday

The morning begins with a 9.00 am laboratory meeting. I hold joint laboratory meetings with Annmarie. Today one of her group is talking – Richard Varcoe is a Wellcome Trust Clinical Research Fellow studying the role of $P2X_7$ receptors in endothelial cell function. He has become the resident expert on quantitative RT-PCR and, as usual, I learn a lot from his presentation.

The meeting is followed by an appointment with a visitor who wishes to discuss the possibility of a position in Manchester, and then by a meeting with Liz Seward, another staff member in the Institute of Molecular Physiology. Liz and I are jointly supervising a new PhD student and we sit with him together to look over his recordings of ATP-induced currents from PC12 cells transfected to express P2X receptors. It is known that these

Figure 3. Tribute to the alma mater. The University of Aberdeen has awarded Alan BSc (physiology), MB ChB (medicine), PhD (pharmacology) and (illustrated here) hononary DSc degrees.

cells have a native channel that is very likely homomeric $P2X_2$, and the student has found that this can be readily suppressed by transfection of a 'dominant-negative' $P2X_2$ subunit carrying a point mutation in its ATP binding site. We are trying to devise experiments that will allow us to use this finding to determine the normal trafficking cycle of the native subunits.

But at 11.30 am a taxi is waiting. Off to Manchester again. I have taken a new position there as Vice-President and Dean of the Faculty of Life Sciences. Although it does not start until 1 July 2004, the merger of the University with UMIST has thrown up some issues that cannot wait. Today it is the appointment of Associate Deans for Research and for Teaching. The meetings are billed as 'interviews', a notion that I rather dislike. I see it more as a dialogue to try to persuade the best people to give up some of their research time to help with the substantial administrative load imposed largely by outside (i.e. government) forces. This reminds me how antediluvian I find the whole procedure for recruiting academic staff in UK institutions. I have been thoroughly influenced by my 18 years in US academia, and find mildly absurd the notion that people are being considered in competition for posts with the pathetic salaries and the meagre facilities generally on offer in the UK. Choosing one's colleagues is by far the single most important aspect of the professional life of any senior academic: it can only be done by a series of one-on-one meetings to identify the best candidate and then providing him or her with every possible reason to join. It cannot be done by a 40 minute revolving door series of interviews.

By the time the meeting ends I have no time for the planned beer with a few of my future colleagues before journeying home. The good news here is that the train stops in Dore before reaching Sheffield; by alighting here I can take a 10 min walk and arrive home at 7 pm.

Saturday

The snow covered ground dissuades me from the ideas of a run along one of the nearby 'edges' – the rocky gritstone cliffs that border many of the nearby moors. The great attraction of life in Sheffield is undoubtedly the proximity to the Peak district with its wealth of walks through open country. Often on a weekend morning I run along the cliff top trails. These are the same gritstone crags that influenced my teenage years, and turned me towards a life that for many years involved exploring the world's distant mountain ranges. This love of mountains was an important reason for studying medicine, since a medical degree is a ready passport to expedition climbing. My interest in physiology developed as an out-growth of the medical curriculum, driven primarily by my frustration at the lack of quantitative thinking in biology but also influenced by a fortunate interaction with Hans Kosterlitz who was one of my physiology teachers in Aberdeen (before he became Head of Pharmacology).

So, instead of running and walking over the moors today I head into the laboratory for a few hours to finish off the revisions of another manuscript. This one is a re-submission for the *British Journal of Pharmacology*; after 2 months of further experiments we hope that it might now be acceptable. No special dispensations for Editors-in-Chief.

The only other person in the laboratory this Saturday afternoon is our American visitor Jim Galligan. He is an autonomic physiologist with substantial programmes back home in gastrointestinal motility and the innervation of veins, and some years ago he identified ATP as a transmitter between neurons in the wall of the intestine. In Sheffield he is recording currents through P2X receptors expressed in HEK cells, and happy with the ability to be able to do experiments undisturbed at the weekend. I drop him off on my way home at around 6.00 pm. He's coming over to our house for dinner tomorrow evening, which means I'd better stop by the grocery/liquor store... but then tomorrow is another week.

Alan North
President, The Physiological Society

Council activities

The agenda for the February meeting of Council included future IUPS meetings, the Aurora mission to Mars and the follow up to the strategy discussions held at the last meeting. The Council agreed that a bid should be made to host the IUPS meeting in 2013. Hosting such a meeting is quite an undertaking, as the venue would need to hold at least 4000 delegates. However, it will fit well with the new policy of having one main meeting a year, and we are grateful to the Meetings Secretary, Bridget Lumb, for coordinating the working party which will draft the proposal.

Mike Rennie brought the attention of the Council to the lack of bioscience input into the Aurora Mission to Mars. He suggested that a significant lobbying effort should be directed to make research councils and government aware of the need for physiological research before the mission. He offered to take the lead on this, which the Council gratefully accepted.

At the Council meeting last November strategy break out groups discussed, among other things, relationships with societies overseas. At the February meeting the Society's president Alan North reported that he has initiated contact with John Williams, Chairman of the American Physiological Society. I will keep you updated with progress in this area.

Some of the rest of the meeting was devoted to housekeeping issues, including the move of the London office at the end of April. I trust the administration staff will be happy in their new accommodation, the address for which can be found on the website.

Dafydd Walters
Chairman of the Executive Committee

Halt on Cambridge primate centre

Nancy Rothwell considers what it means for the future of UK research

'We need to be more active to the violent actions of a small number of protestors' - Nancy Rothwell

The proposed new primate centre at Cambridge University has attracted much publicity. The Deputy Prime Minister granted planning permission, in spite of protests from animal rights groups, and the basic funding was in place through the award of a JIF bid. But the University of Cambridge decided, after considerable deliberations, not to go ahead. Their decision is understandable. Aside from the significant increase in capital costs, the University had to think about the ongoing security costs and the implications of continuing protests for the University and its neighbours. This was probably an inevitable decision, but a very sad one, not only for British research but also for democracy.

There is no doubt that primates, as our nearest relatives in the animal kingdom, elicit great concern when they are used for biomedical experiments. That concern is shared by the public and by many scientists, including myself. For these reasons legislation on the use of primates is the most stringent. Some research simply cannot move forward without the use of a small number of primates. It is this type of research which is being considered in Cambridge – peer-reviewed, considered carefully by local ethical review, and which would benefit, like the animals it requires, from a new facility. The University of Cambridge cannot endanger its staff and students, cause disruption to local inhabitants or deploy excessive police time, let alone meet the extra projected costs which would inevitably detract from other important research projects. Perhaps it was ambitious to plan a stand-alone primate facility, and it may be helpful to develop such facilities close to smaller units in the research laboratories involved – though in many cases this will attract significant additional costs for management and welfare support.

Recent MORI polls suggest that the vast majority of the British public supports animal experiments – provided rigorous controls are in place. A recent BBC poll attracted over 400,000 votes and found that 93% supported the use of animals in biomedical research. So how can a major research facility be halted in its tracks? The protests against Huntington Life Sciences (HLS, the contract research company located quite close to Cambridge) have featured heavily in the news. SHAC (Stop Huntington Animal Cruelty) has mounted an extensive and sustained campaign to close HLS, involving threatening, abusive and sometimes violent behaviour, not only towards HLS employees, but also against its investors and customers. Thanks to the resilience of its staff and strong government support, HLS remains open and SHAC appears to have failed in its bid to close the company and in gaining widespread public support.

But a new organisation, Stop Primate Experiments at Cambridge (SPEAC), which probably includes many of the members or supporters of SHAC, has found a new target – the proposed Cambridge primate centre. Unlike companies, universities cannot mount extensive security because they are open places of teaching and learning for thousands of students. The vast majority of members (staff and students) of any university will have little in-depth knowledge of how and why animal experiments are conducted and of the strict legislation in place.

The questions now are what does this mean for Cambridge, for animal research in other universities and for UK science in general? SPEAC/SHAC have claimed victory and a new target – the University. The current government, and our Minister for Science in particular, has been outspoken in its support for biomedical research and for the need to use animals. They now need to ensure that legislation is in place and is fully implemented to prevent the harassment of anyone linked with such research. Even when violence is not used, continual threats to scientists, their families, their friends and their neighbours are extremely disturbing.

But the government and the law alone cannot solve this problem. The scientific community has a role and a responsibility. For understandable reasons, only a handful of scientists speak or write publicly about animal research. Knowing the huge public support from many recent polls (completely verified by my own extensive experience of talking to children and the public about such issues), we must all participate more. We are unlikely to change the opinions of extremists, but by gaining the support of a large proportion of UK society we can win the argument.

This article was written on a British Council visit to India. I was surprised when they asked me to talk about experiments on animals and antivivisection groups. This is a small but growing problem in India where many animals are held sacred. My message was that the solution is largely in the hands of the scientific community who should devote some of their precious time to public communication.

Avoiding repetition of the unfortunate events in Cambridge is also partly in our hands. We need to be more active rather than responsive or even passive to the violent actions of a small number of protestors.

Nancy Rothwell

MRC Professor, University of Manchester and Chairman, Biosciences Federation Animal Science Group

From magnetic moments to medical imaging

Austin Elliott talks with Paul Lauterbur, American chemist and joint winner of the Nobel Prize for Physiology or Medicine, 2003 for his work on magnetic resonance imaging (MRI)

Austin Elliott (AE) Did you and [British Laureate] Peter Mansfield actually do some of the work together? In Britain it was implied in some news stories that you did.

Paul Lauterbur (PL) No, that's not true. At one time it was very useful to visit Nottingham, not only because Peter Mansfield was there - who I could talk to a little, but we never worked together - but Raymond Andrew* was also there, [although] he was a rather high and mighty professor and dean who did not talk to mere mortals in general.

The only intense interaction I had with Peter Mansfield was when we were trying to arrange a fellowship for a junior member of the Department. I had to carry out the negotiations between Raymond Andrew and Peter, who did not get along well, but worked in the same department. So I went from Peter's office to another part of the building to talk to Raymond and then tried to negotiate back and forth, which at the time I likened to negotiations between Israel and Egypt.

AE So when did you first become aware of Peter Mansfield and his work then, just through reading papers?

PL I heard that he had made some sort of a presentation, in Tallinn in Estonia, late in 1973, from a colleague who had been at a physics meeting there. It was reported that [Peter Mansfield's work] was similar to mine, but it was clear Peter had never read my paper – he doesn't read the contemporary literature in any case, and was very shocked and surprised that there was something similar in press! It was clear from reading Peter's first papers that [his work] came from completely different sources than mine, so they were truly independent ideas in that sense.

* E Raymond Andrew FRS (1921-2001), NMR Pioneer and Professor of Physics in Nottingham 1964-1983

Paul Lauterbur and his wife, the physiologist Joan Dawson, pictured in London in December 2003 en route to the Nobel Ceremony in Stockholm. Both have worked at the University of Illinois in Urbana since 1985. Paul Lauterbur was previously at SUNY Stony Brook, while Joan Dawson was Lecturer in Physiology at UCL where she worked on muscle metabolism (using P-31 NMR) together with the late Doug Wilkie.

AE That's what I had always thought – that you were two people working independently, but towards similar ends.

PL His ideas came more from his work on complex pulse sequences to do [NMR] spectroscopic work on solids and mine came from work on ordinary high resolution NMR. [Our work] partly converged later but was quite different then.

AE What did you actually start out trying to do, as opposed to what you ended up doing?

PL The incentive to develop the ideas [came from] witnessing some studies of rat tumours by a group from Johns Hopkins University. They were doing something which didn't bother them at all - sacrificing rats and cutting out little pieces of various tissues –and there was speculation going around that this sort of thing could be used to characterise tissue, particularly malignant tissue. As a mere chemist I thought it rather strange that people would envisage a medical procedure in which to diagnose your problem they would cut you up. I was a little bit aware that something like that was done with biopsy samples and microscopic characterisation by pathologists, but I thought [that] was likely to be much more characteristic of infiltration by tumour cells in detail than a broad overall number that referred to the condition of a piece of tissue.

[So] I was observing these experiments, which were somewhat tricky and difficult technically because they relied upon [a kind of NMR technique which was] notoriously susceptible to artefacts of various sorts. There was a laboratory that had done earlier work on behalf of Dr [Raymond] Damadian and I was not at all sure whether the numbers were valid - not because of the people involved but because the techniques involved were those I knew easily gave a source of errors. When I observed these experiments in person [and] saw the results on the machine, I also saw there were large differences in the signals from various tissues as well as those from pathological conditions. And I was thinking that it would be much more promising to follow up on such work if it could be done by taking measurements within a living animal or human being instead of on locally cut-up samples. While thinking about that in the evening of that first day, I realised there was something in principle that would enable you to perhaps achieve that end. But there were many questions to be asked and answered, and so I thought it was a very promising insight but didn't know that it could actually be a technique yet. And then it occurred to me that there was a chance that it could be made into a practical technique.

AE That almost counts as a kind of 'Eureka' moment.

PL That moment was over dinner that night, having a hamburger in a local fast food restaurant with a friend. I did suddenly realise that there was the beginning of an idea that might be developed into something useful. Not that no-one else had ever used magnetic field gradients before in a one-

dimensional way, very specific to the [particular] experiment and with no intimation of generality in the process. But from the very beginning I was thinking of it as a general process, actually. Although the citations often refer to two-dimensional [imaging], that was a more practical way than the natural three-dimensional procedure which was not as easy to implement both technically and mathematically. [Two-dimensional imaging] was really a stop-gap solution.

AE Did you ever identify later a single moment when you knew it was going to work?

PL No, more a moment - which didn't feel like a really big moment - of realising there was a principle that could be built on to do this. But after that it was a matter of thinking through each of the things that would have to be done if it were to be a practical technique, and that was spread over a period of several weeks at least.

I don't remember all the details, it was just a matter of working away at the various problems which presented themselves, rather than writing down things as a permanent record for history.

AE In England now people debate a lot whether you can get funded for an idea for a technique as opposed to solving a scientific question. Was it easy to get funded to pursue this?

PL For the first work I did it myself on an existing [NMR] machine in the department, so just my time was involved. Later the first funding was through a mechanism that the NIH had at the time in which they would give a certain small fraction of the institution's NIH grants to the institution to spread around in whatever way it thought was useful for the early stages of research. So I got probably overall $1000 or $2000 or something from that for very minor things - it was all very cheap at the beginning. All the early tests and the mathematical ideas were done on paper with square grids in which I carried out the mathematics by hand - which again was just my time. There was no funding involved. I remember doing some of those calculations while sitting in dull seminars. I am sure the speaker was very flattered to see someone sitting in the audience looking up at the board occasionally and vigorously writing on a pad of paper, but he didn't know what I was writing – nothing to do with the seminar!

It was not until I succeeded in getting some actual results, working in my spare time, that I applied for some NIH grant money. The reviewers of the grant, according to what they told me later, said 'this all sounds crazy'. On the other hand 'all his other work has been reasonable and normal, so maybe there is more to this than we think'. So they adjourned for the night and went back and looked at my proposal again the next day and decided that maybe there was something to it – they didn't know quite what. So, essentially, my previous work led to serious consideration of what might have been dismissed without further thought, so that was fortunate for me.

A similar thing happened when I submitted the first manuscript to *Nature*. It was quickly returned and I wrote a long letter of protest to *Nature* that they hadn't understood it. They

Nuclear magnetic resonance, MRI and the Nobels

Nuclear magnetic resonance (NMR) was originally developed in the mid 1940s, and won the American physicists Bloch and Purcell the Nobel Physics Prize in 1952.

NMR relies on the magnetic properties of certain atomic nuclei, including protons. When placed in a strong magnetic field, the nuclei can orient themselves with or against the applied field, giving states with different energies. Transitions between these states can be induced by irradiating the sample with radio-frequency energy. The excited state can then emit energy, which as in other kinds of spectroscopy has a characteristic frequency. This frequency depends on the applied magnetic field (typically 0.5-2 Tesla for imaging and up to 60 Tesla for spectroscopy – for comparison the earth's magnetic field is about 5×10^{-4} Tesla!) and also on the 'local chemical environment' of the particular proton.

The detailed magnetic properties of the protons in water vary in different kinds of living tissue because of subtle differences in the physical state of water. A key early observation was that the so-called 'NMR relaxation times' (an important magnetic property) of water protons differed between tumours and normal tissues (Damadian, 1971)

Magnetic resonance imaging (MRI) makes use of the inter-tissue variations in magnetic properties of water protons – which explains why different soft tissues look different in MR images. Most critically, MRI depends on being able to assign a signal to a specific point in a three-dimensional sample like a living tissue. The key is to put time-dependent magnetic field gradients across the sample, which gives any given point (or more correctly volume element) in the sample a unique magnetic 'signature'. Complex mathematical algorithms can then be used to reconstruct the image.

As the Nobel web site explains (http://www.nobel.se/medicine/laureates/2003/press.html): 'Paul auterbur…discovered the possibility of creating a two-dimensional picture by introducing gradients into the magnetic field.' Lauterbur published the first two-dimensional MR image in *Nature* (Lauterbur, 1973)

British co-winner Peter Mansfield 'further developed the utilization of gradients… he showed how the signals could be mathematically analysed… (and) also showed how extremely fast imaging could be achievable.'

Over 60 million investigations with MRI are now performed a year worldwide.

References

Damadian R (1971). *Science* 171: 1151-1153.
Lauterbur PC (1973). *Nature* 242: 190-191.

apparently took another look, assigned it to another reviewer and this reviewer said almost the same as the NIH had done - that I had done good things before, although this seemed crazy. He didn't understand why it was of significance, but essentially thought it should be published,.

There was a similar reaction on the part of people who were given the job by my university of deciding whether or not to patent ideas that were submitted as candidates for patents. They decided that the chance it would ever make any money was much less than the cost of applying for a patent and therefore rejected it. But for that decision we might be holding this interview on my yacht off the Riviera! The scepticism in many quarters was very natural considering what most people (in NMR) were doing and thinking. I don't mean to imply that these people were unusually lacking in appreciation of new work or were afraid of the unusual. At one time a research fellow working in my own laboratory, actually doing imaging, came into my office one morning, all dishevelled and upset, saying 'it can't work, it can't work'. After calming him down, I tried to explain why his concerns were irrelevant to its working. But he was a trained physicist and could prove to me that it wouldn't work, even though he was doing it!

There were various other incidents like that, when people with a great deal of experience and good reputations in magnetic resonance claimed that it could not work, or couldn't be true. [This was because of] reasons people had in their minds that seemed good enough reasons to them but were not actually relevant to the problems that I was working on. That of course is why the problem was still there for me to work on about a quarter of a century after NMR was [first] developed. It was the mental barriers that people had in the way of seeing the possibilities of making images with the signals that had preserved the problem so that I would have a chance to work on it.

AE Of all the scientific and medical applications of MRI there are now, which has surprised you the most?

PL I am surprised by two things and for two different reasons. One is so-called functional MRI and looking at brain activation in various regions. From very early on I thought there might be some physiological change in [active] regions of the brain which might show up in magnetic resonance, but the way in which it developed is quite surprising and the extent to which it is used now is very gratifying. The other was the extent to which heart imaging has become possible, because of the heart being a moving organ, - at least as long as the patient is in a condition where diagnosis is helpful! The idea that [MRI] techniques could be used effectively for a moving part of an organism was something we worked on very early on but it has evolved in a most gratifying way, further than I thought it could go.

AE The growth in use of the technology in medicine is amazing. Are you surprised by its extent?

PL About the practical applications. First of all it is hard to say whether I am surprised or not about the worldwide extent. Obviously if it worked out at all it would get wide usage. On the technical side the almost universal use of superconducting magnets for human whole body imaging has been a surprise.

At the time I originally thought of these ideas it was not even certain if *any* kind of magnet could be made with the properties necessary for doing such an experiment. That superconducting devices could be scaled up to that size was surprising for a couple of reasons, one technical, the other financial. It took a while for the potential usefulness of the developments and the improvement in the technology for making superconducting magnets to come together and produce the useful devices that we now know. I remember at one time visiting a manufacturer that had done research on, and built, superconducting devices and meeting there a very senior engineer who was practically in tears. He said: 'I have been working in this field all my life and nothing has ever worked out - except this. This has worked so well, and is so useful to the world, that I feel that my whole life was not wasted'.

AE I believe that there are now scanners you can stand up in.

PL Whether that will be of any practical use for anyone, no-one knows yet. What has had an impact is the designs that provide a more open environment than the usual tube that gives many people claustrophobic reactions. The designs work at lower field but provide more room to look around during the procedures; 'a mother can hold her child's hand' like the adverts say, and larger people can fit into them. The mainstream MRI scanners were deliberately engineered to be as economical and practical as possible. Sort of like aircraft seats, which to save money are made a little bit small for most people. So [scanning anyone] over average size is difficult - athletes, pregnant women, overweight people, or just those who have the misfortune to grow up a bit larger than most of us. What new designs for magnets in general will be accepted by the medical profession and be practical I don't know. My reason for scepticism about the vertical walk-in design is that for most purposes it is desirable to have the patient very quiet – it is a lot easier to be quiet lying down than standing and fidgeting. The combination of fast scanning by using Peter Mansfield's techniques, and very high field magnets for greater sensitivity, could make unconventional arrangements more practical, but this is for the future to decide.

AE Many of the stories about Peter Mansfield in England have emphasised that one of the things that is unusual about him is that he didn't go straight to university, but had a kind of technical engineering apprenticeship background.

PL I didn't know this about Peter Mansfield until I read the newspapers recently. After my undergraduate degree I went to work directly in a research institute instead of going to graduate school because, for one thing, I had had enough of sitting in lectures and listening to professors. I couldn't actually imagine ever being a professor,

and then I was turned into one later. But at the research institute where I worked you could also take classes at the same time at the University of Pittsburgh graduate school and so I began working part-time on a graduate degree at Pittsburgh and shortly after I started on that there was a diversion when I was drafted into the army for about two years.

When I returned to graduate school I continued to work on my degree part-time. The professor I was working with on a joint programme between chemistry and physics – he was in physics, I was in chemistry – decided he was bored with the research he was doing and left the University. So I was left without a graduate advisor. Since no-one else was interested in the work I was doing, my department head very kindly offered to allow me to continue [and said] he would continue to take care of the necessary official documentation, while I just supervised my own research, which he had no confidence in himself. So I did most of my research without a graduate supervisor. My work attracted notice and eventually I almost received a job offer from a major university [until] someone there found out I didn't have a [Ph.D.] degree, and the job offer never materialized. This brought home to me that I should get my credentials. So I finished up my thesis by stapling together a number of publications I already had and ended up with a graduate degree. At the same time I was being considered for a number of other jobs, industrial and academic, and someone from industry asked me why I would chose to take this academic job when I could have a much more interesting and challenging job in industry. I told them simply that if I took the academic job it would be because in a [university] position I could do any silly thing I wanted to do rather than the job the company had for me. And eventually I did, which worked out very well.

AE Where did you serve in the US army, and what did you do?

PL I was classified by the army in one sense as a misfit. They had people with graduate degrees, people with high test scores in the entrance examination, people who were almost illiterate. We received only an abbreviated basic training, then I was assigned, because of my degree and experience, to the Army Chemical Centre, which was devoted to chemical warfare and related topics.

Some [of us] had been drafted in the middle of graduate school, so we worked in the army laboratories where our nominal superiors were civil servants who in general did not have modern training and experience because they had been hired some years before. Because the people they were drafting were very much up to date, those people de facto ran the operation, although they had to get official permission for everything they did.

While I was there the army acquired an NMR spectrometer, [apparently] because they happened to have unspent in the budget at the end of the fiscal year just enough money to buy one. Having leftover money in a Government budget is not something to be taken lightly, as generally you will have that much cut out of next year's budget. So there was an urgent need to spend it in a hurry, and they spent it all on an NMR machine. I found out from one of my friends in the barracks that this was happening [and] because I had some connection with reading and seminars about NMR - but no practical experience - I was able to get myself assigned to that laboratory…

AE And the rest is history.

PL Well, I still had to get some practical experience! Parts of the machine were immediately returned to the manufacturers [to be upgraded]. While I was waiting for the parts to be returned I did as complete a survey as I could of the literature, which at that time consisted almost entirely of work by physicists on the magnetic moments of nuclei and added up to perhaps 400 references on punch cards. This gave me more background than I had before.

When the parts came back I had a chance to do some practical experimental work on chemical warfare agents which was a bit dangerous but provided some interesting moments scientifically as well.

AE You have won a lot of awards and been honoured before in various ways – I remember there used to be a picture on your office wall of you with President Reagan. Of course, the Nobel must be special ...

Joan Dawson No, that picture was on my wall!

PL I was told for many years that the work was certainly a candidate for a Nobel but that could be said of many things and many people. Stories get around that you have been nominated, though you are never supposed to hear, but people gossip. I knew that I had been nominated, but that is very different from actually being awarded the prize, so when Joan took the telephone call in October at 3.30 in the morning it was a surprise. Not a surprise that it ever happened, but a surprise that it had happened this year. There is a lot of good work and a lot of good people out there, and the Nobel Committee can only honour a few.

AE Has it changed your life?

PL It has changed Joan's life!

Joan Dawson I have not had a moment since that call early in October! Paul does not have a secretary or admin assistant so I have been trying to take care of all the arrangements, keep track of all the reporters, get back to them, and so on.

PL Yes it has involved about 200% of Joan's time.

AE Last question. Have you had to have a protocol lesson about meeting the King of Sweden?

PL We have a Nobel Attendant and get a 'walk through' for all of it. They assign someone to each Laureate to make sure you don't wander away or do something wrong. Who knows what can happen to a stranger in Stockholm if they are not watched!

Can a single bout of exercise prevent decompression sickness?

A single session of high-intensity exercise may form the basis for a novel approach to greatly reducing the risk of decompression sickness




Above, from the left: Ulrik Wisløff, Russell Richardson, Zeljko Dujic and Alf Brubakk

Decompression sickness (DCS) following diving, during un-pressurized aircraft flight or space flight extravehicular activity is believed to be initiated by the formation of gas bubbles in the tissue and blood. Nitrogen dissolves in the blood during dives, but comes out of solution if divers return to normal pressure too rapidly - like bubbles coming out of champagne when the bottle is uncorked. The predominant theory is that bubbles grow from preformed nuclei composed of small (approx. 1 micron) stable gas bubbles (Yount & Strauss, 1982). Nitrogen bubbles may cause effects ranging from skin rashes to seizures, coma and death. Even though the risk of DCS is minimized by changing the composition of the gas that is breathed and gradual decompression, DCS can still occur unpredictably. Exercise has long been considered an additional risk factor for DCS, but recent studies in our laboratory (Wisløff & Brubakk, 2001; Wisløff *et al.* 2003; Wisløff *et al.* 2004; *Dujic et al*. 2004) indicates that this notion needs updating.

During diving, gas must be breathed at ambient pressure and tissue equilibrates with the elevated inspired inert gas partial pressure forming a reservoir for bubble growth; with exercise, tissues that receive increased blood flow equilibrate more rapidly. By a separate mechanism, exercise following diving or shortly before or after decompression to altitude can promote bubble formation (e.g. Dervay *et al.* 2001). Exercise during the days preceding diving has received little attention. There are three animal studies (mice, pigs and rats) and all reveal that several weeks of daily aerobic training dramatically reduces the incidence of severe DCS (e.g. Wisløff & Brubakk, 2001). These studies have postulated rheological changes that alter the susceptibility to DCS, modified tissue perfusion, and reduced body fat (in which nitrogen is more soluble). None of these mechanisms are convincing, particularly in light of the findings that a single bout of exercise is equally effective as a longer training regimen and produces a short-term (1-2 days) reduction in decompression-induced bubble formation (Wisløff & Brubakk, 2001).

'Good' and 'bad' exercise?

Initially we found that nitrogen bubbles only formed in the blood of unfit rats. However, by chance we noticed that one bout of exercise 20 h prior to the dive was just as beneficial as 6 weeks of exercise training. Fit rats sent on dives 2 days after stopping exercise developed as many bubbles as unfit rats. Thus, there was no beneficial effect of pre-dive exercise if the exercise was performed too close (e.g. 0.5h, 5h and 10 h), or too far in advance (e.g. 48 h) of the dive time (Wisløff *et al.* 2004). Furthermore, in agreement with Dervey *et al.* (2001), unpublished results from our laboratory suggest that exercise immediately prior to a dive promotes bubble formation. Thus, there seems to be 'good' exercise and 'bad' exercise. Recently we confirmed that a single bout of strenuous exercise 24 h before a dive to 18 m of seawater significantly reduced the average number of bubbles in the pulmonary artery in man, and that there was no correlation between aerobic capacity and amount of bubble formation (Dujic *et al*. 2004). Preliminary data from our laboratory also indicate that only strenuous exercise has a protective effect.

Mechanisms

We currently think that nitric oxide (NO) influences bubble formation and thus is involved in the development of DCS. The body produces NO during exercise; it is crucial for regulating breathing and blood flow, and there is evidence that NO 'makes the inner surface of blood vessels more slippery'. Nitrogen bubbles are seeded like crystals on rough surfaces: the smoother the blood vessels, the harder it is for bubbles to form. If the NO-production is blocked we observe a substantial increase in bubble formation; however, exercise still gives protection despite NO-blockade, suggesting that there is more than just

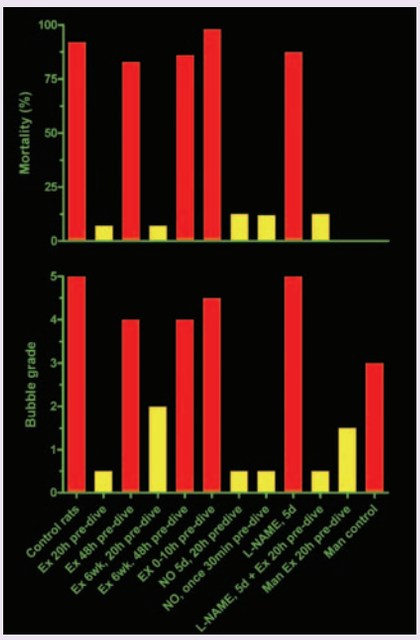


Figure 1 summarizes data for bubble formation and incidence of death after a single bout of interval running or chronic exercise (Ex), Nitric oxide donation (NO) or inhibition (L-NAME), at different time points preceeding a simulated dive. Ex 48h pre-dive indicate that the single exercise bout was performed 48 hours before starting the simulated dive. Ex 6wk, 48h pre-dive indicates that the last exercise bout of chronic endurance training for 6 weeks (5d per week) was performed 48 hours before the dive, etc. For details see references. Data are presented as median of all our data for the respective groups.

NO involved. Furthermore, both chronic and acute administration of an NO-donor protects against bubble formation and death in rats (Wisløff *et al*. 2003; 2004) without performing exercise. We speculate that both exercise and NO hinder bubble formation via alterations in vascular endothelial properties since preexisting gas nuclei are probably attached to the endothelium, where they grow into bubbles that are dislodged into the blood stream. However, if the mechanism of exercise-induced suppression of bubble formation is related solely to nitric oxide production, then the timing of NO administration in relation to its prophylactic effects on bubble formation might be expected to be similar. We recently reported (Wisløff *et al*. 2004) that administration of an NO-releasing agent reduced bubble formation even when given 30 min prior to hyperbaric exposure (without any exercise). Thus, the timing of the responses to exercise and NO administration were quite different (as exercise just prior to a dive was 'bad exercise'), indicating that it is probably not NO alone that results in the exercise-induced protection.

An alternative explanation is that exercise may have a direct effect on micronuclei. Exercise before decompression can enhance bubble formation, but the effect is only temporary, decaying with a half-life of approximately 1 h in humans (Dervay *et al.* 2002). It is likely that micronuclei are activated but the resulting micro-bubbles dissolve if decompression does not occur during their lifetime. Since only a fraction of dissolving bubbles decay into gas micronuclei that can be reactivated into bubbles, it is possible that exercise without decompression depletes the population of micronuclei. Regeneration of the primordial micronuclei population may take 10-100 h (Yount, 1982), and this could explain the temporary protection against bubble formation.

Concluding remarks

Whether or not the effect of exercise on bubble formation operates through the formation of NO as we hypothesize, or through yet another mechanism, the present studies significantly advance our understanding of the effects of pre-dive exercise, and provide another means of ameliorating the formation of bubbles upon decompression in humans.

Since bubble formation is associated with decompression sickness, the studies (Wisløff & Brubakk 2001; Wisløff *et al*. 2003; 2004; Dujic *et al*. 2004) may impact broadly on the field of diving physiology. This work potentially effects a large number of the world's population; in addition to pilots and diving professionals who are at risk of DCS as a consequence of occupation, there are an estimated 854,000 new certifications for SCUBA divers issued worldwide each year.

At this point our data indicate that both timing of exercise and exercise intensity is critical. Before pre-dive exercise can be widely adopted as a predictable safeguard against DCS we will need further standardization and studies. For instance, we need a better understanding of how much exercise is necessary to provide a given degree of protection, and we must develop tools to tell whether we are protected or not before diving. The understanding of the mechanisms involved is, in our opinion, critical as this may ultimately allow us to prevent DCS by biochemical means.

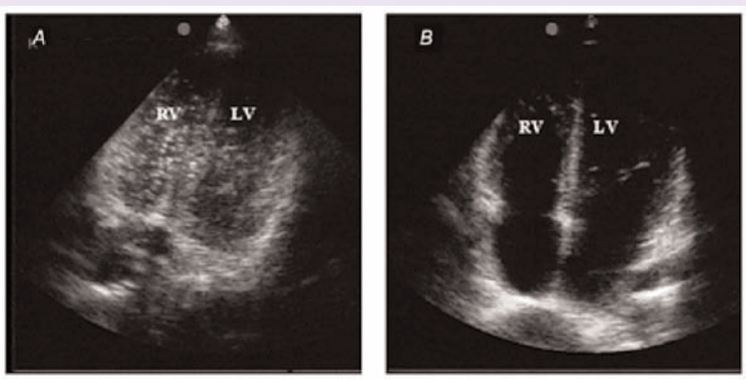


Figure 2. The figure depicts change in venous gas bubbles within the right heart and pulmonary artery following a dive without (A) and with (B) a previous bout of strenuous exercise in one diver. In A, there are numerous, clearly visible venous gas bubbles. After performing the exercise, bubbles are completely absent (B).

Ulrik Wisløff[1,2*]
Russell S. Richardson[1,3]
Zeljko Dujic[4]
Alf O. Brubakk[1]

[1]Department of Circulation and Medical Imaging, Norwegian University of Science and Technology
[2] Department of Cardiology, St. Olavs Hospital, Trondheim, Norway, Faculty of Medicine, Medical Technology Center, Trondheim, Norway
[3]Department of Medicine, University of California San Diego, La Jolla, CA, USA
4 Department of Physiology and Biophysics, University of Split School of Medicine, Split, Croatia
ulrik.wisloff@medisin.ntnu.no

References

Dervay JP, Powell MR, Butler B, & Fife CE (2002). The effect of exercise and rest duration on the generation of venous gas bubbles at altitude. *Aviat Space Environ Med* 73, 22-27.

Wisloff U & Brubakk AO (2001). Aerobic endurance training reduces bubble formation and increases survival in rats exposed to hyperbaric pressure. Journal of Physiology, 537, 607 – 611.

Dujic Z, Duplancic D, Marinovic-Terzic I, Bakovic D, Ivancev V, Valic Z, Eterovic D, Petri N, Wisloff U, Brubakk AO (2004). Aerobic exercise before diving reduce venous gas bubbles formation in human. J Physiol. 555: 637-642

Wisloff U, Richardson RS, Brubakk AO (2004). Exercise and nitric oxide prevent bubble formation: A novel approach to the prevention of decompression sickness? J Physiol. 555: 825-829

Wisloff U, Richardson RS, Brubakk AO. (2003). NOS inhibition increases bubble formation and reduces survival in sedentary but not exercised rats. J Physiol. 546:577-82.

Yount D & Strauss R (1982). On the evolution, generation and regeneration of gas cavitation nuclei. *J Acoust Soc AM* 65, 1431-1439.

Yount D (1982). Journal of the Acoustical Society of America 71, 1473-1481

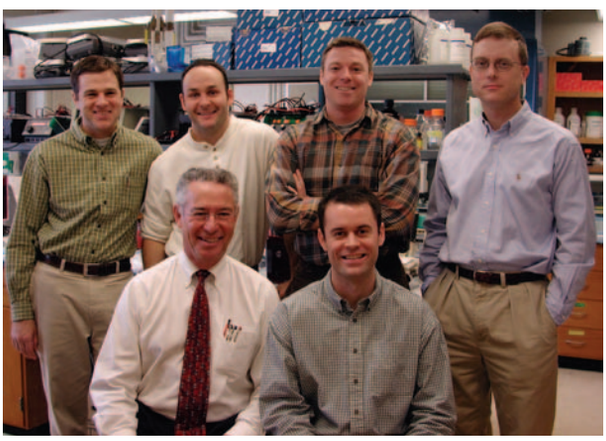
News flash

The original manuscripts discussed in this article and a Perspectives article relating to them, published in *The Journal of Physiology* (**555**, 637-642, 825-829 and 588), formed the basis of the first press release circulated by the Society's new publisher Blackwell Publishing.

This resulted in articles in *New Scientist* (27 March, p 12) and two online journals - *Medical News Today* (http://www.medicalnewstoday.com) and *WebMDHealth* (http://my.webmd.com)

Understanding skeletal muscle hypertrophy: integration of cell signalling

All physiologists know that muscle activity is necessary to maintain muscle mass. But what are the underlying molecular mechanisms at work in the muscle? Here Douglas Bolster and colleagues offer some insights



Left: front row (left to right): Leonard Jefferson and Douglas Bolster; back row (left to right): David Williamson, Stephen Crozier, Neil Kubica and Scot Kimball. Above: Peter Farrell

The vital importance of skeletal muscle to general health and daily activities is likely taken for granted by most individuals. Skeletal muscle is essential for basic posture, movement, and a variety of metabolic functions. Specifically, skeletal muscle accounts for approximately 40 - 50% of the total body mass, serves as the predominant site for glucose metabolism and greatly contributes to the basal metabolic rate. Maintaining or even enhancing skeletal muscle mass becomes critical in the context of aging (sarcopenia) and various disease states associated with muscle loss (e.g. sepsis, cancer, diabetes, HIV). Thus, considerable efforts have been made recently to elucidate the cellular and molecular mechanisms by which skeletal muscle loss (atrophy) and gain (hypertrophy) occur. Importantly, the processes that invoke muscle atrophy are relatively unique and do not appear to be the simple reverse of hypertrophy.

Increases in skeletal muscle mass are dictated through the process of protein turnover, which is the balance between protein synthesis and protein breakdown. Higher rates of protein synthesis relative to protein degradation must be maintained in order to achieve hypertrophy, whereas elevated protein breakdown will induce a loss of protein. Overall, these processes continuously operate and are susceptible to external modulation by factors such as nutrient availability, hormones, and exercise.

Molecular regulation of growth

The molecular controls that govern changes in protein synthesis and eventual gain in muscle mass incorporate both transcriptional and translational inputs. Although exceptions occur, consequences associated with altered gene transcription generally occur over a period of days to weeks, whereas effects attributed to mRNA translation (i.e. the process of synthesizing a protein based on the information encoded by the mRNA) can be manifested within minutes to hours. Transcription and translation each contain three distinct steps (initiation, elongation, termination) with the predominant regulation at the phase of initiation. However, translation is unique because mRNA is recruited rather than produced and this process is responsive to acute metabolic/nutritional alterations. The focus of the present article will be to highlight the impact of mRNA translation initiation on acute changes in protein synthesis, the upregulation of select mRNAs related to growth and how these events culminate to alter gene expression in the context of resistance exercise.

Translation initiation and resistance exercise

Translation initiation essentially encompasses two central components mediated by eukaryotic initiation factors (eIFs) that control rate-limiting events. These two components in simple terms allow the ribosome to bind to the mRNA (eIF4F complex) and to bring the ribosome to the site on the mRNA where translation begins (eIF2/eIF2B) (Fig. 1). An essential mechanism for regulating growth within translation initiation involves the mammalian 'target of rapamycin' (mTOR) protein. Two common downstream targets of mTOR are the 70-kDa ribosomal protein S6 kinase (S6K1) and the eIF4E-binding protein-1 (4E-BP1).

A common misconception regarding changes in translation initiation is that activation of any protein in this pathway corresponds with increases in protein synthesis. For instance, following resistance exercise, elevations in protein synthesis are delayed for several hours while mTOR-

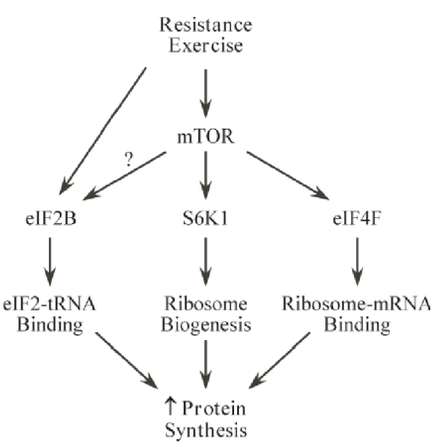


Figure 1. Translational control of skeletal muscle protein synthesis following resistance exercise. Signalling through eIF2/eIF2B appears to control the acute increases in global rates of protein synthesis after resistance exercise. How the mTOR pathway may regulate eIF2B is presently unknown. Activation of S6K1 and eIF4F proteins are mainly responsible for increasing the capacity to synthesize protein with chronic resistance exercise training.

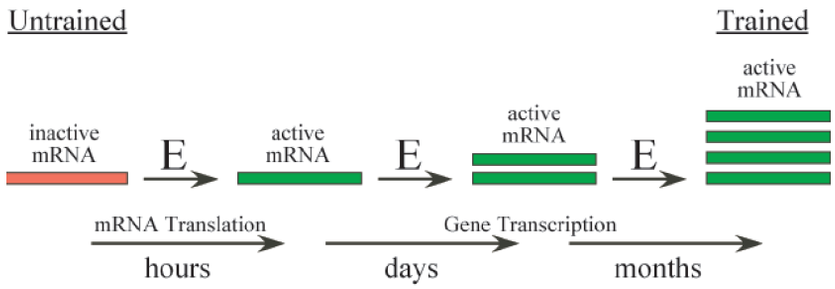


Figure 2. Proposed model of cellular adaptations with resistance exercise. The immediate recovery period following resistance exercise involves translational regulation whereby distinct eIF proteins are activated and specific growth-related mRNAs are upregulated. Repeated bouts of resistance exercise incorporates transcriptional regulation and the specific mRNAs theoretically accumulate and new proteins are synthesized. mRNA translation and transcription operate together to coordinate the eventual increase in skeletal muscle mass. (E: exercise; Inactive mRNA: becomes active following each successive bout of exercise).

mediated events can be rapidly upregulated during this period (Nader & Esser, 2001). Eventual increases in protein synthesis appear to coincide with later eIF2B changes (Farrell *et al.* 1999). Without question, chronic mTOR signalling is indispensable for mediating increased cell size/muscle mass as inhibition of this pathway almost completely blocks the response (Bodine *et al.* 2001). Additionally, the downstream mTOR target, S6K1, is strongly linked with muscle hypertrophy (Baar & Esser, 1999). However, acute suppression of mTOR does not appear to dramatically affect overall rates of protein synthesis in skeletal muscle. Collectively, it is accurate to propose that both components of translation initiation are essential to increases in skeletal muscle mass. Events associated with eIF2B regulation may orchestrate the acute changes in protein synthesis following resistance exercise, whereas activation of mTOR/4E-BP1/S6K1 may result in preferential synthesis of proteins necessary to enhance the translational apparatus and optimize the capacity for protein synthesis with long-term training.

Rapid cell signalling and resistance exercise

Recent efforts to better understand regulation of translation initiation following an acute bout of resistance exercise suggest alterations wherein distinct eIF proteins are rapidly phosphorylated (Bolster *et al.* 2003). Intermittent and transient activation of these proteins may provide more precise control for modulating a growth response. Specifically, these responses appear temporal in nature and the acute impact of resistance exercise on mRNA translation likely becomes cumulative with each successive bout of exercise; the implication being this growth pathway is intermittently turned 'on' with repetitive resistance exercise and distinct mRNAs (ribosomal proteins, etc.) may accumulate to a point where an increase in the amount of specific proteins occurs (Neufer & Dohm, 1993). These responses highlight the longer-term and more rapid control mechanisms associated with transcription and translation, respectively that contribute to achieving muscle hypertrophy (Fig. 2).

Where do we go from here?

Identifying the key factors that rapidly initiate the cascade of signalling events in response to acute resistance exercise remain elusive but several candidates may include integrin activation and/or calcium mobilization. Integrins are transmembrane proteins that couple physical or chemical stimuli to intracellular events, whereas increased calcium flux is evident during muscle contraction. The rapid, yet transient upregulation of the pathway demonstrated by resistance exercise suggests these factors could quickly stimulate mTOR signalling which may then lead to select mRNA translation of local growth factors (i.e. IGF-1), further upregulating the growth response by the cell.

As we look to the future as to how our understanding of muscle hypertrophy will evolve it is important to acknowledge challenges as well. Comparison of data in this area of research is often difficult given the multitude of hypertrophy models currently employed. Tight correlation between cell culture and animal or human data does not always exist. Furthermore, the overlap of various signalling pathways and the rapidly expanding involvement of newly identified proteins makes interpretation complicated. The growth response by the cell incorporates multiple signalling inputs. An integrated response is therefore required and, however tempting, hypertrophy will likely never be isolated to one key protein acting as a 'master switch'. Thus, a multi-faceted approach using genomic, proteomic and bioinformatic tools will be compulsory to elucidate the gaps in our knowledge of how muscle hypertrophy occurs.

Douglas R Bolster[1], Neil Kubica[1], Stephen J Crozier[1], David L Williamson[1], Peter A Farrell[2], Scot R Kimball[1] and Leonard S Jefferson[1]

[1]The Pennsylvania State University College of Medicine, Department of Cellular and Molecular Physiology, Hershey, PA, USA

[2]East Carolina University, Department of Exercise and Sport Science, Greenville, NC, USA

References

Baar K & Esser KA (1999). Phosphorylation of $p70^{S6k}$ correlates with increased skeletal muscle mass following resistance exercise. *Am J Physiol* 276, C120-C127.

Bodine SC, Stitt TN, Gonzalez M, Kline WO, Stover GL, Bauerlein R, Zlotchenko E, Scrimgeour A, Lawrence JC, Glass DJ & Yancopoulous GD (2001). Akt/mTOR pathway is a crucial regulator of skeletal muscle hypertrophy and can prevent muscle atrophy *in vivo*. *Nature Cell Biol* 3, 1014-1019.

Bolster DR, Kubica N, Crozier SJ, Williamson DL, Farrell PA, Kimball SR & Jefferson LS (2003). Immediate response of mammalian target of rapamycin (mTOR)-mediated signalling following acute resistance exercise in rat skeletal muscle. *J Physiol* 553.1, 213-220.

Farrell PA, Fedele MJ, Vary TC, Kimball SR, Lang CH & Jefferson LS (1999). Regulation of protein synthesis after acute resistance exercise in diabetic rats. *Am J Physiol* 276, E721-E727.

Nader GA & Esser KA (2001). Intracellular signaling specificity in skeletal muscle in response to different modes of exercise. *J Appl Physiol* 90, 1936-1942.

Neufer PD & Dohm GL (1993). Exercise induces a transient increase in transcription of the GLUT-4 gene in skeletal muscle. *Am J Physiol Cell Physiol* 265, C1597-1603.

Bidirectional synaptic plasticity and motor learning in the cerebellum

The learning of motor skills – fine movement control – depends upon the conversion of synaptic activity in the cerebellum into longer term changes in synaptic efficacy. Here Françis Crépel and Armelle Rancillac describe how stellate cells play a part

Francis Crépel (left) and Armelle Rancillac

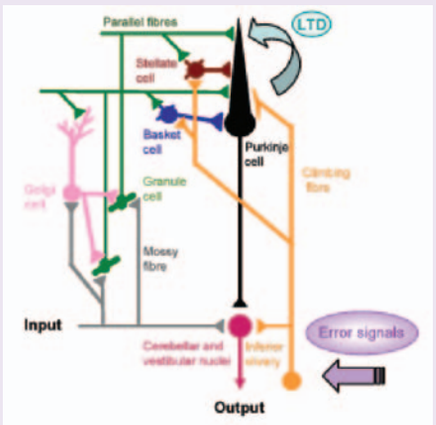
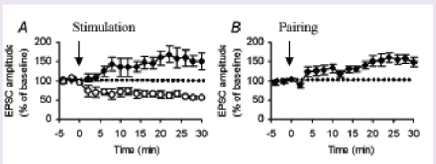


Figure 1. Basic neuronal circuit in the cerebellum. LTD = long-term depression.



C

	Purkinje cells	Stellate cells
Pairing	LTD	LTP
Stimulation	LTP	LTD + LTP

D

	Receptive fields of Purkinje cells	Receptive fields of Stellate cells
Pairing	↓	↑
Stimulation	↑	↓

Figure 2. Synaptic plasticity at PF-SC synapses is induced by stimulation or pairing protocols. A, plots of the amplitudes, against time, of excitatory post-synaptic currents (EPSC) induced in SCs by PF stimulations. At time=0 min, at protocol of stimulation of PFs at low rate (2 Hz for 1 min) was applied. Amplitudes are normalized to their respective control values. Each point is the mean ± sem of 5 separate experiments for LTP (upper plots) and 4 separate experiments for LTD (lower plots). B, same as in A but when a co-activation (i.e. pairing) protocol (see text) was applied at time=0 min (n = 9). Note that LTD is no longer observed and that all plastic cells now express LTP. C, reciprocal bidirectional plasticity of PF synaptic input to PCs and SCs induced by a pairing or a stimulation protocol. D, reciprocal bidirectional plasticity of PF cutaneous receptive fields of PCs and of their afferent interneurones.

Synaptic plasticity and motor learning

Classically, the cerebellum is considered as being devoted to postural adjustments and motor control. In keeping with this view, the geometrical organization of the neuronal network within the cerebellar cortex (see Fig. 1) and the apparent stereotyped properties of its main cellular elements made neurobiologists believe until the 1960s that the cerebellum was a hard wired 'neuronal machine' exquisitely adapted to motor control (Ito, 1984). However, because motor skills can be learnt, the question arose as to whether the cerebellum is able to perform this task, despite its apparent rigid and almost crystalline structure.

As can be seen in Fig. 1, Purkinje cells (PCs) are the only output neurons of the cerebellar cortex. In the late 60s, in keeping with the then current views attributing learning and memory to enduring changes in synaptic efficacy in specific neuronal circuits, Marr and Albus proposed a theory which predicts that when parallel fibres (PFs) and climbing fibres (CFs), i.e. the two excitatory afferents to PCs, are repetitively co-activated at low rate, synapses between PFs and PCs see their efficacy durably depressed, a phenomenon called long-term depression (LTD; Fig. 1). In this system, CFs are thought to carry error signals that instruct PF synapses which were activated during incorrectly performed movements to decrease their efficacy (Ito, 1984). Following early *in vivo* experiments by Masao Ito and colleagues, later *in vitro* experiments fully confirmed this model and unravelled intracellular cascades of events leading to LTD (Daniel *et al.* 1998). Finally, two forms of the inverse phenomenon, i.e. long-term potentiation (LTP) of synaptic transmission between PFs and PCs, can be induced when PFs are stimulated in isolation at low rate (Fig. 2*C*). They differ from one another by the frequency of stimulation required for their induction, and by the underlying intracellular cascades (Lev-Ram *et al.* 2002).

Bidirectional synaptic plasticity in cerebellar interneurones

Other putative sites of synaptic plasticity are present in the cerebellar cortex. In particular, stellate cells (SCs) are inhibitory interneurones which receive the same excitatory afferents as PCs (Fig. 1) and exert on these neurons a powerful inhibition (Ito, 1984). In principle, LTP or LTD at synapses between PFs and SCs should have a long-term counterpart on the inhibitory action exerted by these interneurones on PCs, and thus contribute to long-term changes in cerebellar output during motor learning.

In a recent series of *in vitro* experiments (Rancillac & Crepel, 2004), we showed that, depending on the cells, either LTP or LTD can be induced at PF-SC synapses by repetitive activation of PFs at low rate (Fig. 2*A*). Moreover, pairing this low frequency stimulation with post-synaptic depolarisation of SCs induced a marked shift of synaptic plasticity in favour of LTP (Fig. 2*B*). LTP at PF-SC synapses requires nitric oxide (NO) production as in the case of one of the two forms of LTP at PF-PC synapses (Lev-Ram *et al.* 2002). In contrast, LTD at PF-SC requires activation of G-protein-coupled glutamate receptors. Finally, slightly higher frequencies of PF stimulations induced a cAMP-dependent LTP at PF-SC synapses, like the second form of LTP observed at PF-PC synapses in the same conditions (Lev-Ram *et al.* 2002).

Thus, PF-SC synapses exhibit LTP and LTD which are very similar to those existing at PF-PC synapses with, however, a major difference. At PF-PC synapses, LTD is induced when PFs are activated at low rate in conjunction with stimulation of CFs which strongly depolarize PCs, whereas at PF-SC

synapses, pairing low frequency stimulation of PFs with depolarization of SCs strongly favours LTP. Conversely, at PF-PC synapses, low frequency stimulation of PFs alone induces a NO-dependent form of LTP (Lev-Ram *et al.* 2002), whereas it induces LTD in half of the plastic cells at PF-SC synapses (Fig. 2*C*).

Relevance for motor learning

During motor learning, when co-activation of PFs and CFs leads to LTD at PF-PC synapses, the same co-activation also occurs at the level of SCs, due to collaterals of CFs impinging onto inhibitory interneurones (Fig. 1). Such co-activation is therefore likely to induce LTP at PF-SC synapses, which in turn should potentiate inhibition exerted onto PCs by SCs, and thus reinforce the decrease of responsiveness of PCs due to LTD. Such a synergy between LTP at PF-SC synapses and LTD at PF-PC synapses might therefore play an important role during motor learning. Similarly, LTD elicited at PF-SC synapses by repetitive activation of PFs alone should also work in synergy with LTP induced in PCs in the same conditions.

At a more integrated level, PCs receive information from the periphery. In particular, in the forelimb projection area of the cerebellar cortex, PCs and interneurones receive information through PFs from well delineated and rather small cutaneous areas, i.e. their so called PF cutaneous receptive fields. In an elegant series of *in vivo* experiments, Jörntell and Ekerot (2002) demonstrated that, in this area of the cortex, when PF are electrically stimulated alone or in conjunction with CF stimulations, unpaired PF stimulations induce long-lasting increases in the PF cutaneous receptive field sizes of PCs and induce long-lasting decreases in PF cutaneous receptive field sizes of their afferent interneurones, whereas the inverse is true for paired stimulations (Fig. 2*D*).

This reciprocal bidirectional plasticity of PF cutaneous receptive fields of PCs and of their afferent interneurones fits very well with the bidirectional and reciprocal synaptic plasticity at PF-PC and PF-SC synapses mentioned above (Fig 2*C* and *D*). Besides their importance for understanding how information processing is managed in the cerebellum, such findings might also help to understand how the cerebellum controls motor coordination *per se*. Indeed, an attractive hypothesis proposes that, following signal performance errors transmitted by CFs, the corrective movement components could be initiated or driven by events that activate interneurone receptive fields and braked or terminated by events that activate PC receptive fields (Jörntell & Ekerot, 2002).

Armelle Rancillac
Françis Crépel
UMR CNRS, Paris, France

References

Jörntell H & Ekerot CF (2002). Reciprocal bidirectional plasticity of parallel fiber receptive fields in cerebellar Purkinje cells and their afferent interneurons. *Neuron* 34, 797-806.

Lev-Ram V, Wong ST, Storm DR & Tsien RY (2002). A new form of cerebellar long-term potentiation is postsynaptic and depends on nitric oxide but not cAMP. *Proc Natl Acad Sci USA* 99, 8389-8393.

Ito M (1984). The cerebellum and neural control. New-York, Raven Press, New-York.

Daniel H, Levenes C & Crepel F (1998). Cellular mechanisms of cerebellar LTD. Trends Neurosci 21, 401-407.

Rancillac A & Crepel F (2004). Synapses between parallel fibres and stellate cells express long-term changes in synaptic efficacy in rat cerebellum. *J Physiol (Lond)* 554, 707-720.

Something fishy here? Gramme-atical error? Nano-drolone?

Things were worrying enough for both the Scottish salmon industry (toxicity scares) and tennis player Greg Rusedski (drug accusations) in January this year, but the *Sunday Times* made them a thousand times worse - quite literally. Their article on Scottish salmon (11 January, p. 17) stated that *'the limit for dioxin in fish for human consumption is 4 picograms per gramme. A picogram is a thousand millionth of gram.'* No it isn't; that defines a nanogram, of course. A picogram is a million millionth of a gram(me) - a thousand times smaller than their 'definition'. All the more amusing then that in the Sports section that day (p. 19), discussing Rusedski and nandrolone, Barry Flatman's piece actually had a section headed *'So how much is a nanogram?'* He reported it *'is the equivalent of [sic] one billionth of a gram'*. True, but only provided we are sticking to the (?devalued) US billion, *i.e.* one thousand million, by which their newspaper and most media has long since been seduced. The UK billion is, of course, one million million. So a (UK) billionth of a gram would actually be a picogram.

Using these tiny (or immense) numbers and units requires either more care or should be avoided by the press. When they claim to provide a definition they should please get it right. They make our lives in the universities even more difficult. Here at Glasgow, we had to explain to a first year student last term where to find millimeters on his rule(r). Since we all teach pharmacologists, other bioscientists and medics too - the odd factor of a thousand too little or too much might just prove important – even a matter of life or death!

For criticism of a related, distressingly widespread practice of equating mass and weight, *i.e.* force, in the *scientific* literature, may I refer heavyweight readers to my article *'May the force be with you'* (*Trends in Pharmacological Sciences* (1988), **9**, 124-125). However, I must report that Brian Jewell rightly rubbished my shopping skills for suggesting there that typical Cox's and Bramley's apples are of similar mass.

I am currently pondering the use of the misleading term 'microgravity' that is now a literature commonplace (>5k citations) to describe the situation in spacecraft orbiting the earth. In a straw poll in my 400-strong physiology 2nd year class this session, about half believe(d) that humans would be weightless on the moon. Should we blame the press, or the schools? (See *e.g.* Gürel & Acer, *Astronomical Education Review* (2003), **2,** 3).

David Miller
Institute of Biomedical & Life Sciences
University of Glasgow, Glasgow, UK

The large conductance calcium-activated potassium channel (BK_{Ca}) and the β_2 adrenergic receptor (AR): a direct link to uterine relaxation

The similar pattern of expression between the β_2 adrenoceptor and BK_{Ca} channel during pregnancy suggests that the link between these two proteins may constitute a new piece in the jigsaw

Fiona Broughton Pipkin (left), Boonsri Chanrachakul and Raheela Khan

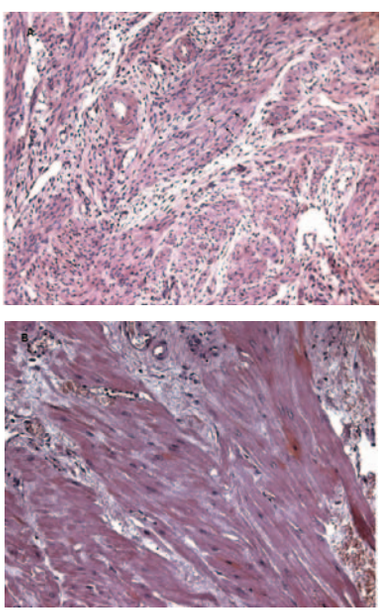


Figure 1. H & E staining of formalin-fixed human myometrium demonstrates, *A* (top) densely packed myometrial cells with small spindle-like nuclei in nonpregnant women whereas, in *B,* cells have a bigger nucleus with more cytoplasm in pregnant women.

Preterm birth, which is the delivery of an infant before 37 completed weeks of gestation, is a leading cause of perinatal mortality and morbidity. It accounts for 6-11% of births and the number is twice as much in developing countries. It is noteworthy that the incidence of preterm delivery has risen in the USA from 9.4% in 1981 to almost 12 % in 2000. This is despite considerable research efforts into the prevention and management of preterm labour. Predictive methods such as ambulatory monitoring and assessment of risk factors have not proved to be reliable indicators in identifying patients at risk.

Preterm birth and its attendant sequelae impose a major burden on health and educational resources, in addition to the emotional and personal costs to families and individuals affected by prematurity. The NHS reportedly spends nearly £40K on each baby weighing < 1000 g (Petrou, 2003). Over £70 million is spent by the NHS each year for neonatal intensive care, even excluding associated health care costs for neurological or respiratory problems. Indirect costs are incalculable arising as a result of, for example, loss of employment to care for a preterm baby.

During the past three decades, the advent of sophisticated medical technologies in neonatal paediatrics has greatly improved the survival rate of premature babies. Indeed, this has pushed prematurity to the extremes of viability and presents its own paradox: survival but at what cost? Babies born at extreme preterm gestations have a good chance of survival but with questionable quality of life. To date, there is no sign of a breakthrough in the prevention or treatment of preterm labour. This may be attributed to our limited knowledge of the complex mechanisms that determine uterine excitability, the quiescence during pregnancy and its physiological removal at term.

The change in size and contractile behaviour of the human uterus with pregnancy is dramatic. Myometrial cells of the gravid uterus are 5-10 times larger compared with their non-pregnant equivalents, due to cellular hypertrophy during pregnancy. This is observed as an increase in size of the nuclei and the amount of cytoplasm in individual cells (Fig. 1*A* and 1*B*). Moreover, the uterus is transformed from a state of relative quiescence during most of gestation to one of powerful rhythmic contractility at parturition determined by an upregulation of contraction-associated proteins (CAPs) such as gap junctions and oxytocin receptors.

The β_2 adrenergic receptor (β_2 AR), a member of the superfamily of G protein-coupled receptors, is abundant in smooth muscle organs. Activation of the β_2 AR results in uterine smooth muscle relaxation. Currently, drugs which act at the β_2 AR, β_2 agonists (ritodrine, terbutaline) are widely used as a main treatment option for preterm

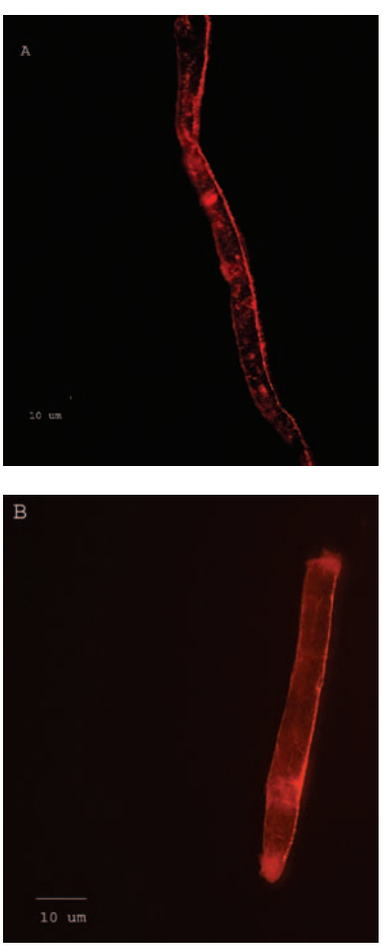


Figure 2. Immunofluorescence of myometrial cells from term pregnant women show that positive staining for (A) 2 AR and (B) BKCa channel is predominantly localized at the plasma membrane.

labour. However, they are associated with adverse maternal cardiovascular and metabolic effects due to the ubiquitous distribution of this receptor in many other target organs. Further, the efficacy of β_2 AR agonists is compounded by the development of tachyphylaxis after continued exposure to these agents both *in vivo* and *in vitro*. Considering this, there is a paucity of information regarding the molecular basis of β_2 AR function in uterine smooth muscles of pregnant women before and after the onset of labour.

We recently reported the plasmalemmal location of β_2 ARs in pregnant human myometrial cells (Fig. 2*A*), levels of which are down-regulated in pregnant women with labour compared with those not in labour (Chanrachakul *et al.* 2003b). However, it remains unclear whether this transition precedes the onset of labour or whether it occurs as a consequence of it.

An increasing body of evidence supports the notion that ion channels may be the terminal effectors in signalling cascades and as such are probably linked to a diversity of specific signalling pathways.

Calcium-activated potassium channels are richly expressed in smooth muscle organs including the human myometrium. Of the three subclasses of calcium-activated potassium channels, the large conductance calcium-activated potassium (BK_{Ca}) channel predominates in human myometrium and is involved in mediating uterine relaxation (Khan *et al.* 1993). The BK_{Ca} channel comprises a pore-forming α subunit and a regulatory β subunit.

Previous data regarding the expression of BK_{Ca} channel mRNA and protein in mouse and rat myometrium showed conflicting results. We demonstrate that, as for β_2 AR, BK_{Ca} channels are predominantly localized to the myometrial cell membrane (Fig. 2*B*) and that levels of both the α and β subunit of the BK_{Ca} channel decline in parallel in myometrial tissues obtained following the onset of labour of both term and preterm pregnancy

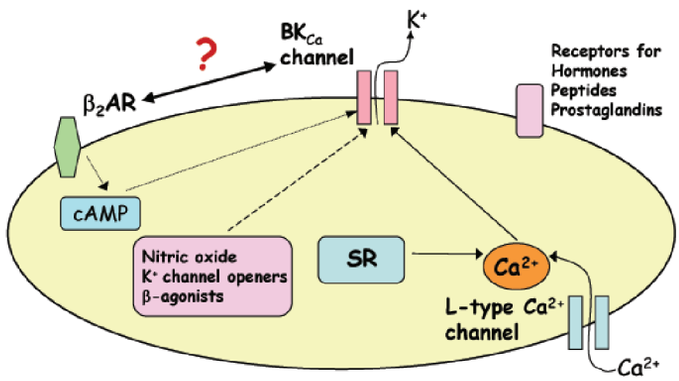


Figure 3. A schematic representation of pathways leading to control of uterine activity. Elevation of intracellular calcium from calcium influx and release from sarcoplasmic reticulum (SR) activates BKCa channels resulting in uterine relaxation. BKCa channels are likely to have an important functional role in 2 AR mediated-relaxation in the human myometrium

(Chanrachakul *et al.* 2003a; Matharoo-Ball *et al.* 2003).

Uterine contractions result from an elevation of intracellular Ca^{2+} which in turn activate BK_{Ca} channels leading to uterine relaxation, but cellular control of this pathway is not fully understood. A prominent feature of β_2 AR stimulation is their linkage to the activation of BK_{Ca} channels (Kume *et al.* 1989). In the human uterus, β_2-agonists activate BK_{Ca} channels causing cellular hyperpolarization via G protein-dependent pathways. However, the molecular basis of the interaction between these two proteins in mediating uterine relaxation and the onset of labour in humans is not known. Interestingly, our recent data suggests that there is an apparent colocalization and a direct protein-protein interaction between the β_2 AR and BK_{Ca} channels in the term, pregnant human myometrium (Chanrachakul *et al.* 2003c).

We consider it to be of significant importance to examine the correlation between β_2 AR and BK_{Ca} channel in much greater detail. Our ongoing studies are focussing on the molecular and functional association between these two entities in human myometrium and their contributions to myometrial relaxation signalling cascades.

Hopefully, these findings will lead to the development of novel therapeutic strategies that target the β_2 AR/BK_{Ca} pathway for the treatment of preterm labour to reduce the incidence of prematurity.

Acknowledgement

Boonsri Chanrachakul is supported by the Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Thailand.

Boonsri Chanrachakul
Fiona Broughton Pipkin
Raheela N Khan

Academic Division of Obstetrics and Gynaecology, School of Human Development, University of Nottingham, Nottingham, UK

References

Chanrachakul B, Matharoo-Ball B, Turner A, Robinson G, Broughton-Pipkin F, Arulkumaran S & Khan RN(2003a). Immunolocalization and protein expression of the alpha subunit of the large-conductance calcium-activated potassium channel in human myometrium. *Reproduction* 126, 43-48.

Chanrachakul B, Matharoo-Ball B, Turner A, Robinson G, Broughton-Pipkin F, Arulkumaran S & Khan RN (2003b). Reduced expression of immunoreactive beta(2)-adrenergic receptor protein in human myometrium with labor. *J Clin Endocrinol Metab* 88, 4997-5001.

Chanrachakul B, Turner A, Matharoo-Ball B, Broughton Pipkin F, Arulkumaran S, Khan R N. (2003c). Colocalization and expression of β_2-adrenergic receptor and large conductance calcium-activated potassium channel in human myometrium. *Proc Phys Soc* 551P, C8.

Khan RN, Smith SK, Morrison JJ & Ashford ML (1993). Properties of large conductance potassium channels in human myometrium during pregnancy and labour. *Proc R Soc Lond B Biol Sci* 251, 9-15.

Kume H, Takagi K, Tokuno H & Tomita T (1989). Regulation of Ca-dependent K-channel activity in tracheal myocytes by phosphorylation. *Nature* 341, 152-154.

Matharoo-Ball B, Ashford ML, Arulkumaran S & Khan RN (2003). Down-regulation of the alpha- and beta-subunits of the calcium-activated potassium channel in human myometrium with parturition. *Biol Reprod* 68, 2135-2141.

Petrou S (2003). Economic consequences of preterm birth and low birthweight. *Bjog* 110, Suppl 20, 17-23.

Imaging the activity of single calcium channels: 'optical patch-clamp recording'

'Total internal reflection' sounds a bit navel-gazing, but is actually a microscope technique that can allow ion flow through single channels to be observed optically. Here Angelo Demuro and Ian Parker explain how

Angelo Demuro (left) and Ian Parker at the finish line of the Badwater Ultramarathon through Death Valley

Ion channels regulate the activity of virtually all cells - both electrically excitable and inexcitable. Our ability to study these channels was revolutionized following the invention of the patch-clamp technique by Erwin Neher and Bert Sakmann (Neher & Sakmann, 1976), which allows currents to be recorded through single channels with exquisite (sub-pA and sub-ms) resolution. Nevertheless, patch-clamping has some limitations. Among them, little or no information is obtained regarding the subcellular distribution of channels; it is not possible to record independently from more than one channel at a time; and trauma associated with giga-seal formation may disrupt the local cytoskeleton and thereby affect channel function. There is also the practical matter that patch-clamping requires a lot of patience – each pipette can be used only once, and in every patch-clamp lab there is an old coffee tin (or nowadays, an officially-approved sharps bin) containing hundreds or thousands of discarded pipettes.

Optical single-channel imaging

For these reasons, there has been much interest in developing optical techniques that could allow us to non-invasively image the activity of numerous individual ion channels within a cell, or even within cells in an intact tissue or organ. One potential method involves the use of fluorescent reporters of protein structure (Sonnleitner *et al.* 2002) – for example, targeted exogenous dyes, or GFP-tagged ion channels – to obtain a readout of conformational changes in channel structure associated with its opening. This has the advantage of providing biophysical information about channel functioning, but faces daunting problems of weak signals and rapid photobleaching because only one, or a few, fluorophore molecules are conjugated to each channel.

An easier approach involves the use of fluorescent probes that sense the ions passing through a channel. This provides a built-in amplification, as thousands of ions per ms typically flow through an open channel – indeed, that is what makes patch-clamp recording possible. Moreover, optical recording offers further gain, because a single fluorophore molecule can emit thousands of photons per millisecond. There is a limitation, however, as to which ions can be sensed, and Ca^{2+} ions are at present the only species for which detection at a single channel level is feasible. In part this is because of the availability of highly sensitive and selective fluorescent Ca^{2+} indicators. More importantly, it also reflects the enormous changes in Ca^{2+} concentration that occur near the mouth of an open Ca^{2+} channel. Since the resting cytosolic [Ca^{2+}] is maintained at a few tens of nM the local concentration can increase 1,000-fold when a Ca^{2+}-permeable channel opens, whereas corresponding changes for ions such as Na^+ or Cl^- are less than 10-fold.

The first unequivocal experiments imaging Ca^{2+} flux through single channels were made by Zou *et al.* (1999), who used widefield fluorescence microscopy in conjunction with whole-cell electrophysiology to show fluorescence signals accompanying openings of individual caffeine-activated channels in the membrane of smooth muscle cells. The temporal and spatial resolution in their records, however, was poor: fluorescence signals rose and fell over a few hundred ms during and after channel openings, and spread over tens of micrometres. This degradation arises simply from the diffusion of Ca^{2+} ions (and of Ca^{2+}-bound indicator molecules) away from the 'point source' of the channel.

Improvements in spatial and kinetic resolution should thus be achieved by restricting fluorescence measurements to the close vicinity of the channel mouth, where changes in [Ca^{2+}] are largest and rapidly track the opening and closing of the channel. Indeed, better results were subsequently obtained using confocal microscopy to monitor fluorescence from sub femtolitre cytosolic volumes (Wang *et al.* 2001; Demuro & Parker, 2003). However, there are practical limitations as to how fast the confocal laser spot can be scanned, necessitating a trade-off between spatial and temporal resolution. Those studies thus used

linescan imaging, in which fluorescence is monitored along only a single line in the cell, typically scanned every 2-8 ms. This has significant disadvantages in that spatial information is restricted to a single dimension, the scan line intersects only a few channels, and distorted signals arise from out-of-focus channels to either side of the scan.

Total internal reflection fluorescence microscopy

To circumvent these limitations we have explored the use of total internal reflection fluorescence microscopy (TIRFM) for rapid two-dimensional imaging of cytosolic Ca^{2+} signals arising very close to the cell membrane (Axelrod, 2003). TIRFM works by directing excitation light through a glass substrate toward an aqueous specimen at a sufficiently shallow angle that total internal reflection occurs due to the refractive index decrease at the glass/water interface. However, a very thin electromagnetic field (evanescent wave) with the same wavelength as the incident light is created in the liquid, and decays exponentially with distance from the interface (typically over one or a few hundred nm). Because this field is able to excite fluorophores near the interface while avoiding excitation further into the aqueous phase, it provides an 'optical sectioning' effect similar to, but even narrower than, that achieved by a confocal microscope.

Although the idea of TIRFM is old, its biological utility has expanded greatly in the last few years with the development of specialized oil-immersion objective lenses with very high numerical aperture (1.45 or greater). These allow the excitation light to be directed to the specimen at the necessarily shallow angle through the very edge of the lens while using a high-sensitivity c.c.d. camera to visualize fluorescence in the evanescent field through the same objective (Fig. 1).

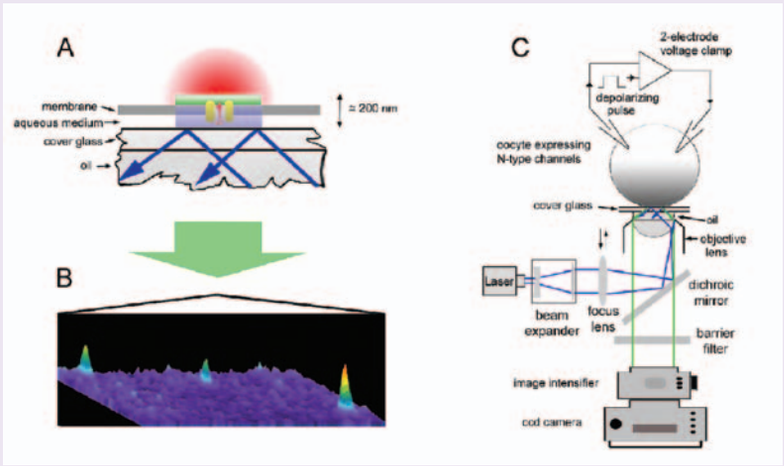


Figure 1. A, principle of TIRFM imaging. Excitation light (blue) from a laser is directed at a shallow angle through a coverglass, so that it undergoes total internal reflection at the interface with an aqueous solution (Ringer's solution). This creates an evanescent field extending ~ 100 nm from the interface, which can excite fluorescence (green) in a dye-loaded cell in close proximity to the coverglass, allowing imaging of the microdomain of Ca^{2+} (red) around the mouth of an open Ca^{2+}-permeable channel. B, pseudocolored representation showing 3 sparklets (single-channel openings) in a 60 μm square region of oocyte membrane. C, schematic of the system used for TIRFM imaging and voltage-clamp activation of Ca^{2+} channels expressed in *Xenopus* oocytes. (adapted from Demuro & Parker, 2004).

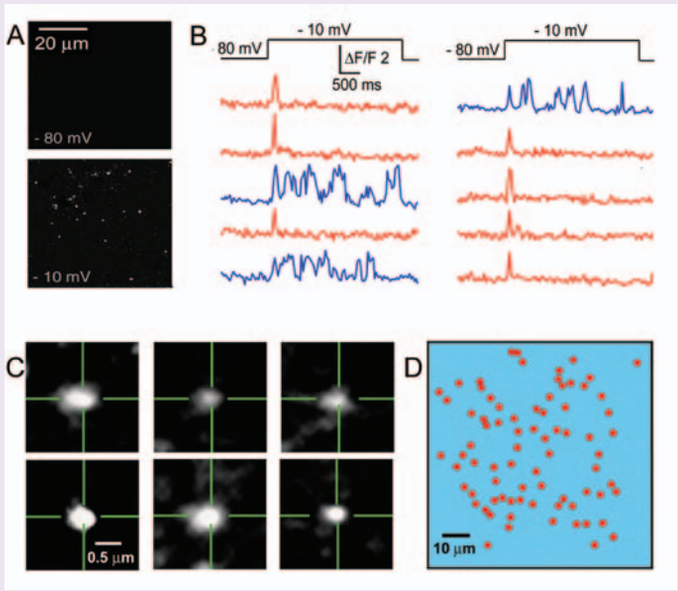


Figure 2. Imaging the activity and localization of single N-type channels expressed in the oocyte membrane. A, single video-frames showing TIRFM fluorescence at rest, and after depolarizing to activate channels. Each spot (sparklet) in the lower panel arises from Ca^{2+} flux through an individual channel. B, measurements of channel gating obtained by recording local fluorescence signals at sparklet sites. Examples are shown of simultaneous recordings from 10 channels. Note the variation in gating properties. Some channels (red) showed only a single, brief opening immediately on depolarization, whereas others (blue) showed continued, longer openings throughout the depolarizing pulse. C, N-type channels are immobile in the oocyte membrane. Panels show high-magnification views of sparklets at a given site during repeated depolarizing pulses over a period of about 5 min. Green crosshairs are centered on the first event. D, map shows the locations of sparklets within a region of membrane.

Imaging Ca^{2+} channels expressed in oocytes

We tested the ability of TIRFM to resolve Ca^{2+} flux through individual N-type voltage-gated Ca^{2+} channels expressed in *Xenopus* oocytes injected with the Ca^{2+} indicator fluo-4 dextran (Demuro & Parker, 2004). After stripping away their surrounding vitelline envelope, oocytes adhere closely to a coverslip, so that the cell membrane and immediately adjacent cytoplasm lie within the evanescent field, with only a thin intervening film of extracellular solution. Depolarizing pulses (applied via a two-electrode voltage clamp) then evoke numerous, transient flashes of fluorescence ('sparklets', Fig. 2*A*). Several lines of evidence indicate that the sparklets reflect openings of single N-type channels: they are absent in control oocytes; their fluorescence magnitudes correspond to expected single-channel

Brain waves plainly speaking

Recent studies of brain waves (oscillations) generated by the hippocampus reveal how a large collection of nerve cells turns into a living brain tissue. These oscillations are brain-specific integrative network activity, adopted through the collective properties of the network, and not supported by the activity of individual cells

Yacov Fischer

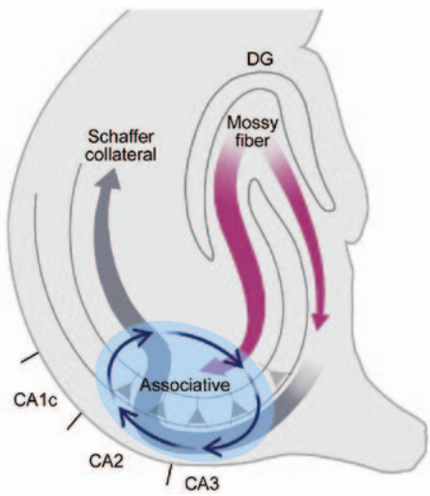


Figure 1. Axonal pathways intrinsic to the hippocampus. Three main intrinsic axonal pathways exist in the hippocampus: the Mossy fiber-, the Schaffer collateral-, and the Associative pathway. In contrast to the other pathways, the associative pathway does not convey information between the hippocampal subfields (DG, CA3, CA2, and CA1). Instead, recent data show that the associative pathway is critical for the adaptation of an oscillatory mode of activity by the hippocampus.

How the brain works remains largely an inaccessible question which we, as researchers, lack the conceptions and tools to address.

However, we can deal with a manageable problem by rephrasing the question to: what characterizes the activity of the living brain, and how does it translate to the functions we assign to the brain? By solving this basic question, we are able to learn important information about the principles that govern the function of a large group of neurons as a living brain tissue, and in turn reach the position where we can think of ways to address more complex questions.

What is the most characteristic function of the brain known? The answer is straightforward – brain waves, known in scientific terms as oscillations. Indeed oscillations, a brain specific phenomenon, are a hallmark of the living brain. Since their discovery, in the late 1920s, oscillations (and the resulting EEG) have been suggested to be involved in a variety of normal activities and pathologies of the brain, and to be critical to many 'higher' brain functions. It is therefore conceivable that oscillations are likely to represent a basic operational principle of the brain and its organs.

Indeed, Grey Walter showed in a series of studies that were ahead of their time (1950s) that robots built to implement the biological principles of oscillations could exhibit self-awareness, consciousness, learning, recognition of other members of the group, and social behaviours.

To address the 'old' and 'new' conceptions regarding oscillations, I shall concentrate only on oscillatory activities that are related to the hippocampus. The hippocampus is particularly suitable for the study of oscillatory activity, since it is the source for theta oscillations (~8 Hz), a prominent brain wave, and contributes to the brain's gamma activity (~40 Hz).

These rhythmicities are a brain-specific integrative network activity that is suggested to be critical to the function of this organ and of the brain. Therefore, understanding the underlying mechanisms would reveal the principles governing the integrative network function (oscillations) of the organized neuronal ensemble (the hippocampus).

'Old' concept

It is believed that the firing pattern of action potentials of the hippocampal cells underlies the oscillatory activity. Action potentials are an all-or-none type of signal that represent a form of a 'decision' at the single cell level that provides the cell with the means to communicate this 'decision' to other cells.

This concept, first discovered in invertebrate neurons, demonstrates that the basic principles of neuronal function are consistent throughout the species. However, in invertebrates, where the nervous system consists of a small number of neurons, the function of every neuron is critical; in the mammalian brain, where neurons are abundant, it is not necessary for every neuron to exhibit action potential firing to support their function.

'New' concepts

Direct measurements of the activity of individual cells of the hippocampal network show that oscillations depend on sustained synaptic activity. It is therefore reasonable to assume that a mechanism based on sustained synaptic activity underlies the EEG signal, rather than an action potential based one.

There is increasing evidence that an action potential-based mechanism does not support the sustained synaptic activity. This is because the numbers of action potentials provided by the principal cells are too low, and the properties of discharge in the inhibitory cells are not always consistent with initiation, frequency-control, synchronization and pacing of the oscillations. This is further illustrated when considering the energy constraints on the tissue, where action potentials consume a large part of the brain's energy, and cannot be sustained at high rates for long.

Gap junctions are likely to be a critical element in the integrative function of the hippocampus to adapt an oscillatory

mode of activity. This notion was brilliantly introduced in the theoretical work of Roger Traub who, without any data, connected the physical entity of the gap junction and the theoretical notions of interactions in large networks to be the element to sustain the interaction in the large network that would influence its own function. This notion is now further supported by physiological, anatomical, and pharmacological correlative data.

The hippocampal associative pathway, one of the large axonal pathways intrinsic to the hippocampus, is the core element underlying the adaptation of the oscillatory mode of activity by the hippocampal network. This pathway, originally discovered by Lorente de Nó in the 1930s, is now found to be one of the central solutions that allows the hippocampus to support an oscillatory mode of activity under physiological conditions. The pathway consists of a large collection of axonal collaterals that unlike other intrinsic pathways does not seem to convey information between different regions of the hippocampus. The mechanism underlying sustained synaptic activity is accounted for through functional activation of this pathway, action potential discharge of contributing cells, and gap junction mediated interactions. Such a mechanism, based on the principles of distributed processing in a large axonal network, formation of a reverberatory system, and existence of a random and distributed probabilistic 'clock', explains how oscillations are initiated, maintained, synchronized, and paced, and how specific patterns are adapted. The solution offered by such a mechanism is robust and supports the idea that the oscillations are important for the natural function of the hippocampus.

With these new concepts, we can see some of the solutions that exist at the network level to support the integrative function of the brain tissue. These are significant breakthroughs in our understanding of the brain and its function. They also demonstrate that studying the principles of integrative function in organized neuronal ensembles is a realistic approach to significantly advance our knowledge, and that neurophysiology and electrophysiology are still among the most powerful tools, when appropriately used, for studying the function of the brain.

Yacov Fischer
Brain Research Institute, University of Zurich, Switzerland (kfischer@hifo.unizh.ch)

References

Attwell D & Laughlin SB (2001). An energy budget for signalling in the grey matter of the brain. J Cereb Blood Flow & Metab 21, 1133-1145.

Fischer Y & Dürr R (2003). Inhibitory control of intrinsic hippocampal oscillations? Brain Res 982, 79-91.

Fischer Y (2004). The hippocampal intrinsic network oscillator. J Physiol 554, 156-174.

Traub RD & Bibbig A (2000). A model of high-frequency ripples in the hippocampus based on synaptic coupling plus axon-axon gap junctions between pyramidal neurons. J Neurosci 20, 2086-2093.

Getting insight into the work of tendons

Oksana Kostyuk and Robert Brown describe how a novel fibre-optic spectroscopic technique based on light-scattering can provide structural information on tendon changes


Oksana Kostyuk (left) and Robert Brown

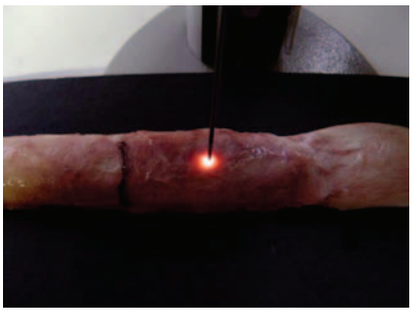
It is amazing how our quest for knowledge goes in circles. People have always used light reflected by skin for diagnostics. Remember those typical questions: 'you look a bit pale today, are you all right?' Or: 'what is that rash, have you got an allergy?' Now science is trying to make use of this ancient knowledge in a more systematic and quantitative way. In our centre we use elastic scattering spectroscopy (ESS). Its basic principle is not as dramatic as it sounds: non-harmful white light is flashed onto the surface of the tissue via an optical fibre and the light that comes back from the tissue is collected by a second fibre for analysis. This 'backscattered' light contains a wealth of information about the composition and structure of the tissue. A major challenge, however, is to understand just what this overwhelming amount of spectral data means and to 'dig up' something useful for diagnostics, for instance to spot early stage skin cancer (Wallace *et al.* 2000). Another example would be to detect early degeneration of the Achilles' tendon, for example, after injuries in footballers.

Tendons are the connective tissues which transmit mechanical forces from muscles to bones. To fulfil this function, a rope-like, tough, fibrous structure has evolved, formed by the well-aligned fibrils of collagen, the most abundant body protein. Such a well-organised structural arrangement is characteristic of a healthy tendon, but it becomes less organised as the tendon degenerates, ages or is injured. Loss of this tight-packed organised structure means that the tendon is weaker, less efficient in transmitting forces and prone to break suddenly. Detecting such changes early, predicting an impending rupture, or following the repair after injury would be equally valuable for humans and, for instance, racehorses. At the moment there is no way to measure structural changes in living tendons non-destructively and certainly not without a hospital and a million pound MRI scanner. Both MRI and ultrasound can provide images showing the size and swelling of the tendon, but such qualitative information needs skilled interpretation and remains largely subjective. In addition, the changes detected with these techniques are probably characteristic of rather later stages of the tendon degeneration.

In our recent paper (Kostyuk *et al.* 2004) we reported how an ESS-based technique was used to non-destructively study structural changes

during in vitro loading of the horse superficial digital flexor tendon, analogues to the human Achilles' tendon. We used the phenomenon of the backscatter anisotropy (unequal distribution) found in tissues formed by aligned fibres like muscle (Marquez *et al.* 1998) or with partial alignment of structural fibres such as skin (Nickel *et al.* 2000). When light was delivered to the surface of a normal tendon sample, an elongated, elliptical 'aura' of light distribution in the tissue was apparent (Fig. 1). Much more backscatter was detected when the probe was positioned parallel to, rather than perpendicular to, the tendon fibres (the probe was held perpendicular to the tendon surface and rotated to achieve different detection angles). To characterise this backscatter anisotropy we calculated an Anisotropy Factor (AF_λ), as a ratio of maximum to minimum intensities of backscatter (at any given wavelength, λ). Where the amount of light travelling in different directions is the same (circle-like 'aura'), this ratio is one, but it increases rapidly as the backscattered 'aura' becomes elliptical. In relaxed tendons the AF_{500} was around 7, but it increased up to 18.5-fold when tendons were stretched in a material testing machine.

Encouraged, we applied ESS to study tendon pathology, investigating matched pairs of horse tendons, one normal and the other clearly degenerated with a pronounced lesion. This pathological change in the tendon structure produced near circular 'aura' of backscatter (Fig. 2). More interestingly, however, even far away from the lesion region of the tendon, the backscatter 'aura' was still rounder than the elliptical one of a normal tendon. The AF_{500} confirmed this



Distribution of light in a matching pair of horse superficial digital flexor tendons: normal (Figure 1, left) and degenerated (Figure 2, right)

impression: it had a value of about 8 for the normal control tendon (similar to the previous study), but in case of the degenerated tendon it was equal to only about 1.2 in the area of the visible lesion and about 2.5 when measured 10 cm away from the lesion. We are now carrying out ultrastructural investigation of these tendons to complement the ESS findings.

Thus, this non-destructive real-time fibre-optical technique can provide structural information on changes in tendons under load or due to pathology. It can be used to study *in situ* physiological structural changes in tendons and ligaments during use (Morgan *et al.* in preparation). It has also proved to be an effective means for monitoring development of the collagen fibril alignment as tissue-engineered constructs matured in culture (Kostyuk & Brown, in press). It seems beyond doubt that ESS-based techniques have huge clinical potential as diagnostic and monitoring tools in medicine and tissue engineering, particularly as ESS seems to be able to 'see' early structural changes in the tissues. Recent advances in fibre-optic technology make it possible to design really thin optical probes that could be applied via an endo/arthroscope or even via a surgical needle. Together with a relatively cheap basic spectroscopic set-up and a simple data analysis algorithm, this technique may represent a major research and diagnostic advance.

Acknowledgements

The authors are grateful to Helen Birch for providing the horse tendon samples and to Mary Morgan for her help with the imaging of the tendons.

Oksana Kostyuk
Robert Brown

Tissue Repair & Engineering Centre
Institute of Orthopaedics
Royal Free and University College Medical School
London, UK

References

Kostyuk O & Brown RA (in press). Novel spectroscopic technique for *in situ* monitoring of collagen fibril alignment in gels. *Biophys J.*

Kostyuk O, Birch HL, Mudera V & Brown RA (2004). Structural changes in loaded tendons can be monitored by a novel spectroscopic technique. *J Physiol* 554, 791-801.

Marquez G, Wang LV, Lin SP, Schwartz JA & Thomsen SL (1998). Anisotropy in the absorption ans scattering spectra of chicken breast tissue. *Appl Optics-OT* 37(4), 798-804.

Nickel S, Hermann M, Essenpreis M, Farrell TJ, Krämer U & Patterson MS (2000). Anisotropy of light propagation in human skin.

Wallace VP, Crawford DC, Mortimer PS, Ott RJ & Bamber JC (2000). Spectrophotometric assessment of pigmented skin lesions: methods and feature selection for evaluation of diagnostic performance. *Phys Med Biol* 45(3), 735-751.

Wonderful

Wonderful: Visions of the Near Future is a different kind of art show – one that questions what it means to be 'wonderful' in this time of rapid technological advance and cultural instability. This major new project emerges from the timely discussions and realizations of artists and scientists working together collaboratively to investigate and create shared experiences and discoveries. The project is a Wellcome Trust and National Endowment for Science, Technology and Arts (NESTA) collaboration, with additional support from Arts Council England, and has been inspired by today's artistic and scientific developments, suggesting possible futures as they may be in 5, 10 or 100 years.

These are not the utopian or distopian visions of science fiction, but the discoveries of artists and scientists working collaboratively to test our responses to ethical questions and to develop industrial prototypes based on concepts taken from art.

Exhibition dates are:

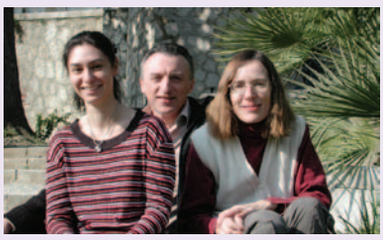
18 September-1 October, 2004 – Magna, Rotherham

28 November, 2004-9 January, 2005 – Cornerhouse, Manchester

Contact: Maria Fusco, Press Consultant for *Wonderful*
Tel: 07720 775 093
Email: press@wonderfulwebsite.net
Website: http://www.wonderfulwebsite.net

Vasopressin may limit its own secretion with the help of pituicytes

Vasopressin released from the pituitary is a critical controller of body water balance. Like many hormones, it seems to be able to inhibit its own release. Jean-Marc Mienville and colleagues discuss the possible underlying mechanisms



Lia Rosso (left), Jean-Marc Mienville (centre) and Brigitta Peteri-Brunbäck

To maintain homeostasis, organisms often resort to various mechanisms of negative feedback. This is particularly true of secretory processes, a classical example being the output of catecholamines, which is self-regulated through inhibition of tyrosine hydroxylase (the enzyme that catalyzes the first step of catecholamine synthesis) by each intermediate product of the synthetic chain.

Recently, we have obtained evidence in support of yet another type of negative feedback involving a crosstalk between the neuronal and glial components of the neurohypophysis (Rosso *et al.* 2004). This gland comprises primarily three functional entities: the axon terminals of the hypothalamic magnocellular neurones that synthesize and secrete the hormones vasopressin and oxytocin; pituicytes (the glial component); and blood vessels, which drain the hormones from the sites of release and allow them to reach their cellular targets through the general circulation. Here we describe how vasopressin may regulate its own output by acting upon pituicytes, the specialized astrocytes of the neurohypophysis.

Since the late 1950s, work from several laboratories has suggested that pituicytes might be involved in the regulation of hormone secretion from the neurohypophysis. This idea was generated by electron microscopy studies indicating profound morphological changes in pituicytes during physiological states that involve a high output of neurohypophysial hormones. Numerous converging data led Hatton (1988) to propose a model whereby activated pituicytes retract both from between secretory terminals, thereby increasing their excitability, and away from the basal lamina of the perivascular space, whose increased contact with terminals ought to facilitate hormone release into the blood. Both vasopressin and oxytocin are synthesized in the magnocellular nuclei of the hypothalamus; they are axonally transported to the neurohypophysis where they are released into the blood. Vasopressin (or anti-diuretic hormone) plays a crucial role, among others, in the hydromineral balance of the organism by favouring water reabsorption by the kidney. Its output is primarily regulated by the electrical activity of magnocellular neurones. During dehydration, for example, the firing of these neurones is increased via activation of peripheral, central and intrinsic osmoreceptors sensing a rise in plasma osmolarity (see Bourque *et al.* 1994 for review). At the neurohypophysial level, this increased activity propagates to vasopressinergic axon terminals whose secretory vesicles release their content into the blood.

Relevant to our findings, two particular features of this secretion are (1) the fact that it also occurs within the interstitial space of the neurohypophysis, and (2) that ATP is present in the vesicles (see Rosso *et al.* 2004 for details). As a consequence, pituicytes are likely to be exposed to both vasopressin and ATP every time secretion is activated.

Because ATP is quickly broken down to adenosine by specific enzymes present in the neurohypophysis, we investigated whether the latter compound could be one of the signals involved in the morphological changes observed in pituicytes. Using *in vitro* cultures, we found that adenosine was indeed capable of dramatically modifying pituicyte shape from a flat and fusiform aspect to a shrunken cell body surrounded by long processes, a phenomenon called stellation (Rosso *et al.* 2002a). We are currently in the process of verifying whether this also occurs *in vivo*. Subsequently, we discovered that vasopressin was able to reverse stellation, bringing pituicytes back to their basal shape (Fig. 1; Rosso *et al.* 2002b). If ATP and vasopressin are coreleased within the pituicyte environment, what could be the net

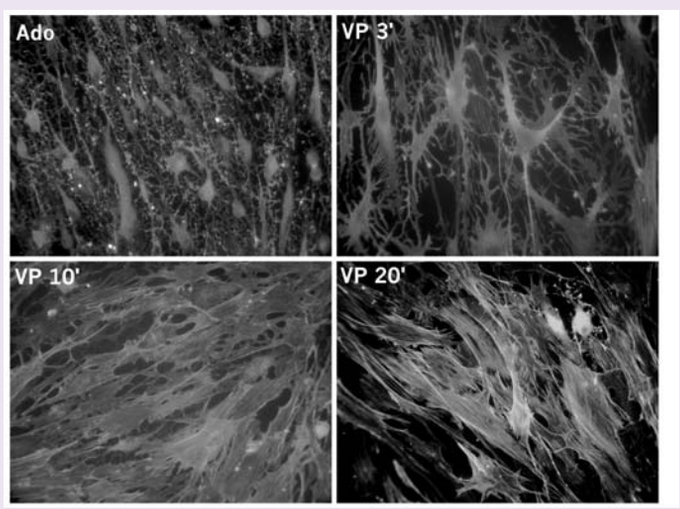


Figure 1. Time-dependent (in min) changes in pituicyte morphology elicited by vasopressin (VP; 10 nM) and revealed by F-actin immunofluorescence. The cells were initially stellate due to the presence of adenosine (Ado; 10 μM) in the culture medium.

effect of two simultaneous signals having opposite actions? Our provisional hypothesis is that during the initial stages of secretion vasopressin receptors are internalized – and thus non-functional – due to the high concentrations of vasopressin 'seen' by the cells. This idea is borne out both by previous observations in various cell types and by our own unpublished data. Therefore, we believe that the purinergic effect (chemically both ATP and adenosine are purine compounds) initially prevails, and that adenosine-induced stellation *in vitro* corresponds to the morphological changes observed *in vivo* upon activation of the hypothalamo-neurohypophysial system. It should be noted that stellation reversal can be elicited by very low vasopressin concentrations (EC_{50} ~0.1 nM), so that following hormone clearance and/or adenosine breakdown, vasopressin might be able to negatively feedback on its own secretion by returning pituicytes to their resting morphology.

A second component of this putative negative feedback consists of the ability of vasopressin to release taurine from pituicytes. Taurine is known as an ubiquitous osmolyte in the regulation of cell volume, but its role in the neurohypophysis has more of a signalling nature, inasmuch as it inhibits vasopressin release by activating strychnine-sensitive glycine receptors located on neurohypophysial terminals (reviewed by Hussy, 2002). Here, the physiological significance is straightforward given the fact that hypotonic shocks increase taurine

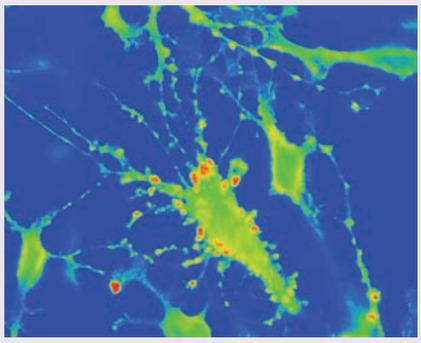


Figure 2. Selective concentration of taurine in pericellular protrusions 1 min after 10 nM vasopressin application. Pseudo colours represent varying fluorescence intensity of anti-taurine antibody from low (blue) to high (red) levels (from Rosso *et al.* 2004).

levels in the isolated neurohypophysis, which is consistent with the need to keep vasopressin levels low under these conditions. We, in turn, have demonstrated that vasopressin itself is capable of inducing pituicytes to release taurine, again suggesting a negative feedback mechanism for self-limitation of secretion (Rosso *et al.* 2004).

An intriguing aspect of vasopressin's action on pituicytes was the formation of cellular protrusions intensely stained for taurine (Fig. 2). The nature and physiological role of these protrusions remain to be established. One important functional parameter of the taurine-releasing effect of vasopressin is that it is prevented in hypertonic conditions. Therefore, one can reason that during the initial stages of hormone demand, e.g. during dehydration, vasopressin will be unable to release taurine because of the hyperosmotic environment of the neurohypophysis, thereby allowing unimpeded output and full action of the hormone. Thereafter, when the water balance begins to be restored and the need for vasopressin subsides, a powerful negative feedback can be activated via taurine-induced blockade of release, which may help terminate the action of vasopressin and prevent water overload.

Most of these results were obtained *in vitro*. If they are confirmed *in vivo*, they will provide another example for the use of a negative feedback mechanism in the control of the organism's secretions. Furthermore, such a mechanism would represent a novel physiological role for neuron/glia interactions.

Lia Rosso
Brigitta Peteri-Brunbäck
Jean-Marc Mienville

CNRS – UMR 6548, Laboratoire de Physiologie Cellulaire et Moléculaire
Université de Nice-Sophia Antipolis, Nice, France

References

Bourque CW, Oliet SH & Richard D (1994). Osmoreceptors, osmoreception, and osmoregulation. *Front Neuroendocrinol* 15, 231-274.

Hatton GI (1988). Pituicytes, glia and control of terminal secretion. *J Exp Biol* 139, 67-79.

Hussy N (2002). Glial cells in the hypothalamo-neurohypophysial system: key elements of the regulation of neuronal electrical and secretory activity. *Prog Brain Res* 139, 95-112.

Rosso L, Peteri-Brunbäck B, Vouret-Craviari V, Deroanne C, Troadec J-D, Thirion S, Van Obberghen-Schilling E & Mienville J-M (2002a). RhoA inhibition is a key step in pituicyte stellation induced by A_1-type adenosine receptor activation. *Glia* 38, 351-362.

Rosso L, Peteri-Brunbäck B, Vouret-Craviari V, Deroanne C, Van Obberghen-Schilling E & Mienville J-M (2002b). Vasopressin and oxytocin reverse adenosine-induced pituicyte stellation via calcium-dependent activation of Cdc42. *Eur J Neurosci* 16, 2324-2332.

Rosso L, Peteri-Brunbäck B, Poujeol P, Hussy N & Mienville J-M (2004). Vasopressin-induced taurine efflux from rat pituicytes: a potential negative feedback for hormone secretion. *J Physiol* 554, 731-742.

Journals for Iraq

A Cambridge student, wounded while filming in Baghdad in July, has launched a drive to help restock Iraq's universities with books and journals. Raeid Jewad, a PhD student at Darwin College, hopes that people will donate journals, reference books, dictionaries and works of literature. He says that the British Council will handle the shipping of books and journals and he has discussed their distribution within Iraq with the Ministry of Higher Education and Scientific Research. John Agresto, who heads the Ministry, says that almost none of the professors in Iraq's universities have visited a research university in their field outside Iraq. In many classes textbooks are either non-existent or more than 20 years old and access to contemporary books and journals is therefore a priority. Anyone who might be able to help can contact Raeid Jewad by email at: iraq@cusu.cam.ac.uk

Right: Maggie Leggett (the Society's Deputy Executive Secretary) married James Relf (former Society facilities, grants and membership officer) on 27 February.

Qualia and private languages

Denis Noble explains the 'private language argument', where philosophy and neurobiology meet head-on

Denis Noble

Since writing the Foreword to *Philosophical Foundations of Neuroscience* (Bennett & Hacker, 2003), I have been asked to explain the 'private language argument' in terms more familiar to scientists than the dense tomes of Wittgensteinian philosophy.

The argument lies at the core of a set of philosophical puzzles, so one can encounter it in various guises. Let's take an example of such a puzzle. The protagonists in my story are called ME and YOU for convenience and all you need to know about them is that they have the same mother.

While I am writing this document, I look closely at the print. I note that it is black and the page is white. So, I tell you that I am currently writing this with a black font on a white background. You reply that, yes, you understand what I have told you, but you nevertheless have a nagging doubt.

You express this by saying 'How do you know that I see black, or white, as you do? Perhaps, what I see when I receive your email is what you would see as blue on pink, or green on ultramarine, or any one of millions of possible combinations, including colours that perhaps you have never seen! The only restriction is that the form of the relations between my perceived colours and yours must be such that we always agree on what to call what we see. We use the same names, but we may see differently.'

Naively, I respond initially by saying 'don't be silly, we both learnt what it means to refer to black and white at our mother's knee!'[1]

YOU: Oh yes, of course, but that is not what I mean. When we learnt at our mother's knee, I thought we were all looking at the same things and must see them in the same way. Since then I've read some philosophy and neuroscience and I can't for the life of me see how anyone else, even our mother, could know what I am seeing when I look at a black font. My experiences are inside me, inside my head, in my brain, and no-one else can see them. I may see the world completely differently from the way you see it.

ME: Oh dear, you've become quite a solipsist recently. I also feel like that sometimes. Don't worry, it will pass. Let's have a curry together.

YOU: No, no, it won't pass, you really don't understand. I am serious. I am me. You are you. You can't know what I experience in my own private world.

ME: Where on earth is that?

YOU: Don't play games with me. You can't see inside my head.

ME: Well, actually, I can. We can record from your neurons, scan your brain for blood flow changes, and many other things. We would find inside your head much the same stuff that you would find in mine.

YOU: Yes, I know that. I don't think I am different because I am made differently – though equally obviously we are not physically identical. It's just that … well, I am me, and you are you. Don't you see?

ME: Yes, I certainly see that, but I don't see why that entitles you to say that you have a private world that I can't know about.

YOU: Look, this is getting exasperating. Obviously I am not referring to my neurons, or my blood flow changes, or anything else of a physical nature. I am referring to these sensory experiences that I have. You know, they even have a name now. People call them 'qualia'.[2] You must also have them. Just look at one of those letters on the page. There is a black on white quale there!

ME: So you have become a dualist? You think there is something there that is not physical?

YOU: Oh no, not at all! These things are created by my neuronal processes, perhaps in a sense they *are* my neuronal processes – or at least what it feels like to have them. We are not going back to Cartesian dualism. I am not supposing a soul that interacts with my brain. In fact I just think that I am my brain. And my brain creates these experiences that I see, feel, hear.[3]

ME: I thought that these experiences were created in the same world that both you and I live in, which is why I was puzzled about reference to 'your private world'.

YOU: Well, yes, that's sort of true. But I am not referring to the things in the world itself. I am referring to the *quality* of the sensations I have when I see the world. That's why they are called qualia.

ME: So, wait a minute. When you look at a black font, you think that there is not only the black font itself but also

[1] Actually, this move is not as naïve as it may initially appear – see the denouement of this story.

[2] This term was originally introduced by 20th century philosophers to refer to the 'qualitative character of experience'. The singular is 'quale'.

[3] This stage of the argument could have been the departure point for another version of the private language puzzle. The protagonist, ME, could have asked what on earth the 'I' was doing in this sentence. It would take another version of the dialogue to explore the problems created by this way of speaking about the relationship between the self and the brain. This illustrates the point that there is a set of puzzles here that are all inter-related by various versions of the private language argument.

something else that is inside your head?

YOU: Yes, you've got it. I wish I could have put it that way myself.

ME: But that's just another form of dualism. Why do you need to suppose that there is anything inside your head other than the neuronal processes that occur when you see a black font?

YOU: No, wait a minute. I don't think these qualia are a different sort of substance, something ethereal and ghostly.

ME: But that's just what it sounds like to me! Tell me this. You are a scientist. You think that your brain is a material thing, though fiendishly complex. What possible experiment can we perform that will confirm whether or not these things that you call qualia exist?

…… long silence …….

ME: Well?

YOU: Well, it's not like that. As I said before, you can't know what I experience, so I can't tell you.

ME: 'So, what do you do? Do you, as it were, tell yourself – perform a kind of self-talk? How do you compare your own experiences?

YOU: Of course, that's easy. I know what I mean when I refer to black and I can remember what it was like. So, in a sense, I can tell myself 'this is black'.

ME: But you can't tell me?! You must have a private language.

YOU: Well, if you want to put it that way, I suppose I do. But everyone does.

…… different long silence …….

YOU: Don't you?

ME: Well, I am not sure about this. Tell me, where did you learn this 'private language'? Does it have the same words as our language?

YOU: Well, I hadn't thought much about that. Yes, I suppose it does. At least, when I tell myself that I see black, I don't invent a new word. I don't refer to it as 'kcalb' for example. Actually, (Oh dear, this is getting muddling!), I don't think I use any words at all – I certainly don't need to.

ME: So, this language is neither a different language and, possibly, it isn't even a language at all?

YOU: Well it's certainly not a language as we learnt at our mother's knee. But, look, it's very simple really. I see black. I know I see black. I remind myself that this is the same kind of quale that I have experienced before. If I must put it into words, I suppose I would tell myself 'I am seeing black'.

ME: And when you say that to yourself you also tell yourself that you are communicating something different from what you would communicate to me when you say to me 'I see black?'

YOU: Yes.

ME: So what is it that is different?

YOU: I've already told you. It is the description of the quale, not the font itself – it's how I see it.

ME: But we don't know that they exist. We have no way of conducting an experiment to see whether they exist. So why do you need to refer to qualia? Why not go back to when we learnt language at our mother's knee? When we saw black, mother said 'that is black', so we both got to know that that is what it is called. Isn't that simple? Moreover, we could only do that because all three of us looked at the same pictures in the same book. That's how we came to use the same language. If we had been French we would have called it 'noir', if we were Japanese we would have learnt to say 'kuroi', but we would still have ended up being able to do all that anyone ever can do to communicate what they see when they see black. Mother didn't ask us whether we could see any strange qualia!

YOU: No, but she didn't know any science.

ME: Hey wait a minute. This is not science! We seem to have agreed that what you are talking about is something – qualia – for which we can have no experimental evidence; that you communicate with yourself about seeing these qualia in a language that is either not a language, or just the same language you use to tell me 'I see black'; that we are not talking about there being anything inside your head other than material substances (neurons, blood vessels) of the same kind that I have in my head; so where is the science in this 'private language' stuff?

YOU: OK. I agree that I am expressing a particular philosophical view of the world. But I also think that there are some kinds of philosophical beliefs that are necessary for us to conduct scientific investigation. How could I possibly study the brain-mind problem if I didn't think there were qualia formed as a result of neuronal processes of a certain kind? Goodness me, this is the greatest challenge for neuroscience! You can't convince me that this is all a wild goose chase!

ME: Maybe not, but if I am right then you don't even have a problem. In the sense we are talking about here, there is no mind-brain problem.

YOU: What?!

ME: Well, it's up to you. If you think there is a problem, then there is a problem, but perhaps the problem is the way you are thinking, not a problem for science. You are proposing to investigate a phenomenon for which we can have no experimental evidence; that requires a language that is private – which is a contradiction in terms; languages are for communication – and which leads to a modern form of dualism which I would suggest is alien to what science can seek to know about us as human beings.

YOU: I think we had better have that curry. You will have to tell me what *you* see as the relation between mental and physical events!

Denis Noble
University Laboratory of Physiology, Oxford, UK

Reference

Bennett MR. & Hacker PMS (2003). *Philosophical Foundations of Neuroscience*. Blackwell Publishing, Oxford.

Clinical physiology in Warsaw

Who we are and where we come from

Andrzej Beresewicz (left) and Bohdan Lewartowski, hosts of the joint workshop with the Physiological Society in Warsaw in May

This spring (13-16 May 2004) the Physiological Society is organizing a workshop in cardiovascular physiology entitled '*Signal transduction in cardiovascular system*'. The meeting is primarily intended for young scientists from Central and Eastern European countries. It will be held in Warsaw, and its Polish co-organizer is the Department of Clinical Physiology (DCP) of the Medical Centre of Postgraduate Education (MCPE), an independent academic medical school providing postgraduate education. Outlined below is a brief profile of our department and its history.

DCP is one of the few laboratories in Poland dealing with cardiac (patho)physiology. Our current teaching obligations include 6-7 two-week courses per year (lectures, seminars and laboratory demonstrations on '*physiological bases of clinical cardiology*'), which are obligatory for all physicians specializing in cardiology and cardio surgery (some 150 persons/year). For several years we also taught cardiovascular physiology to undergraduate medical students. Apart from every-day teaching and research, MCPE is also responsible for organization and supervision of the national system of medical specialization by physicians, dentists, and pharmacists.

Historically, medical schools in Poland were always parts of universities. Only after the Second World War did Poland and other Eastern Block countries adopted a so-called 'progressive' pattern of organisation of their academic education, which meant separating faculties of theology, medicine, agriculture and others from their mother-universities and establishing independent educational institutions. Subsequently, undergraduate and postgraduate medical education were institutionally separated and independent postgraduate medical schools were created throughout the communist bloc. MCPE came into being in 1967 as a result of a secession of a part of the Warsaw Medical School. The *idée fixée* of its founders was that it should function and be organized in exactly the same way as other medical schools in Poland (although the students to be taught were already graduates of medical schools). This meant that in addition to various medical departments, which were already available, new basic science departments, including physiology, had to be organized from scratch. Fortunately enough, MCPE was given a brand new building, initially designed as a city hospital, to house its theoretical departments. Physiology got an almost completely equipped operation theatre, a completely empty space originally built for a nephrology ward (nine rooms), and, with one exception, employed very young and completely inexperienced staff.

Bohdan Lewartowski was appointed to organize and head DCP (till 1999, when replaced by Andrzej Beresewicz). At that time he was a young (38) enthusiastic MD, PhD (docent) trained in physiology. He had just returned home after a 6 month stay in the Department of Experimental Cardiology, University of Amsterdam headed by Dirk Durer, and was fascinated by different electrophysiological techniques, including microelectrode recording. It was perhaps this fascination, the availability of surgery facilities, and the team's medical background that determined DCP's scientific interests for subsequent decades. The main topics of the research were: (i) electrophysiology of ischemic heart and cellular mechanisms of cardiac arrhythmias (the topic now abandoned); (ii) the mechanics and energetics of the left ventricle, particularly during regional ischemia (experiments on open-chest dog hearts, also abandoned now); (iii) excitation-contraction

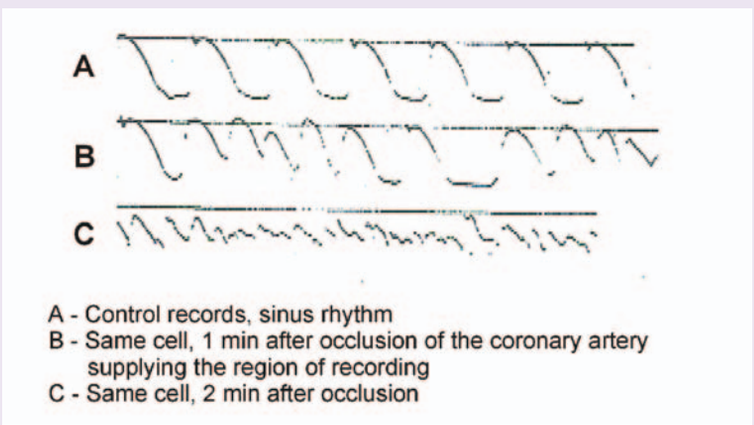


Figure 1. Microelectrode recording of cellular action potentials of the left ventricle of the *in situ* dog heart fibrillating due to occlusion of coronary artery. Reproduced from Czarnecka M, Lewartowski B, Prokopczuk A (1973). *Acta Physiol Pol* 24, 331-337.

coupling under physiological and pathological conditions (role of sarcoplasmic reticulum, mechanism of initiation and maintenance of the tonic component of cardiomyocyte contraction, ECC in heart failure); (iv) mechanisms of myocardial ischemia/reperfusion injury in the models of isolated rat and guinea-pig heart (the role of free radicals, endothelium, nitric oxide and local inflammation); and (v) mechanisms of myocardial and endothelial protection by ischemic preconditioning. It is hardly surprising then that the first original research papers from DCP described effects of propranolol on cellular action potentials in rabbit papillary muscle and dog Purkinje fibres and an original method of ventricular wall tension measurement in dog hearts. To the best of our knowledge, the first published microelectrode recordings of ventricular fibrillation from *in situ* heart (Fig. 1) were done in DCF. Actually, till the late 90s, DCF was the only lab in Poland in which cardiac cellular potentials/currents were recorded. Altogether, approximately 100 original papers in peer-reviewed journals and numerous review articles and book chapters have been published from DCF since its foundation.

The current staff of DCP consists of two professors (one emeritus with part-time appointment), three senior assistants (all of whom obtained their PhD in DCP in last 3 years), three younger assistants (PhD students), and two technicians. Initially most of the staff were MDs (which is important when it comes to the postgraduate teaching of physicians). However, in the last decade the proportion of MDs on the staff has systematically fallen due to poor wages in basic sciences. The salaries were always small but it was a sort of 'travelling privilege' rather than salaries that eventually attracted young people to the basic sciences. Poland was unique among the Soviet Union satellites in that Poles were allowed to travel abroad, and young scientists with a PhD could take post-doc positions in western laboratories. In those days the extremely favourable exchange rates made it everybody's desire to earn money outside the country and spend it at home. Scientists in Poland were offered such a possibility. Now that the exchange rates are no longer so attractive, it is medical practice and/or the pharmaceutical industry, rather than western laboratories, that offer the most favourable earning possibilities.

It was always a rule in DCP that everyone who got his PhD degree was entitled to spend 1-2 years in a foreign lab. Most of us did so (in Holland, Switzerland, Germany, Sweden, the USA, Canada and the UK). This enabled a transfer of new techniques to DCP (e.g. microelectrodes, isolation of cardiomyocytes, voltage clamp technique, intracellular calcium measurements) and allowed us to maintain contacts with the western science and scientists. Probably because of these personal contacts, the European Society for Clinical Investigation invited DCP to organize a 3 day workshop for young European clinicians interested in basic cardiology (1978). Sadly many DCP alumni took the opportunity of being outside the 'iron curtain' and sooner or later emigrated, mostly to the USA. Currently, there are perhaps more former members of DCP working abroad than in Poland. This accounts for a 'generation gap' (deficit of middle-generation scientists) in a majority of scientific institutions in Poland (and perhaps other post-communist countries) and is among the most serious threats for our future scientific development.

Poland and nine other countries are to join the European Union on 1 May, 2004. There are many, often unrealistic, expectations related to this event. One, we believe realistic, is that the easiest part of the job will be to create 'the European Union in Science'. The initiative of the Physiological Society in organising and sponsoring meetings like that in Warsaw seems to support this notion.

Bohdan Lewartowski
Andrzej Beresewicz

Department of Clinical Physiology, Medical Centre of Postgraduate Education, Warsaw, Poland

Why British physiologists should be part of the European Space Programme – and what is stopping us

A major reason why many of us believe passionately in human space physiology is that it is such a sexy subject - Michael Rennie

The European Space Agency has made a commitment to a manned mission to Mars using the Moon as a staging post. Named the 'Aurora Mission', it signals a new dawn in the confidence of European scientists and technologists to take part in this great endeavour – the exploration of our solar system. Unfortunately, Britain so far has had little to offer, mainly because our financial contribution to the European Space Agency is almost entirely based upon those physical sciences and technologies for which the government can see a quick market return, i.e. satellite navigation systems, mobile phones, and earth survey activities including meteorology. In fact Britain puts in less money than Belgium, an astonishing difference when the GNPs of the two countries are considered.

A few of us have been attempting to persuade Lord Sainsbury and others, including Ian Halliday, head of PPARC which takes the lead in space matters (he is fond of saying 'Everything above 100 km is ours') that there are sufficient major benefits to biology in general, and certainly to human physiology, for us to be profitably involved. The space shuttle dealt a dreadful blow to the idea of manned space exploration, but Ian Crawford of UCL has recently argued (*Astronomy & Geophysics*, **45**, 2.28-2.29, (2004),* given that UK participation in Aurora is to be 'science driven', many

scientific disciplines, including the planetary sciences would benefit from the presence of human explorers on the surfaces of the Moon and Mars. There is no substitute for human beings for space exploration because of human versatility, especially the ability to make on the spot decisions and serendipitous discoveries not foreseen in advance. Imagine if the descendants of Captain Fitzroy and Charles Darwin had been on Beagle II – the dog which did not bark in the night. Possibly, all they would have needed to do to restore communications was simply substitute a new circuit card for the one that was malfunctioning.

However, to get to space there are many problems to be overcome. The problem of solar radiation, many fold greater than on earth, is severe, but there are also pathophysiological problems with wasting of muscle and bone. We know from studies of Russian astronauts that a relatively short sojourn in space, 6 months to a year, results in massive loss of bone and muscle mass, and indeed also of cardiac muscle mass. Returning astronauts from the estimated 3 year round trip to Mars could well have lost more than half of their bone and muscle in the process. This is essentially a medical technological problem but it will depend upon the identification of good counter measures which can be used in space.

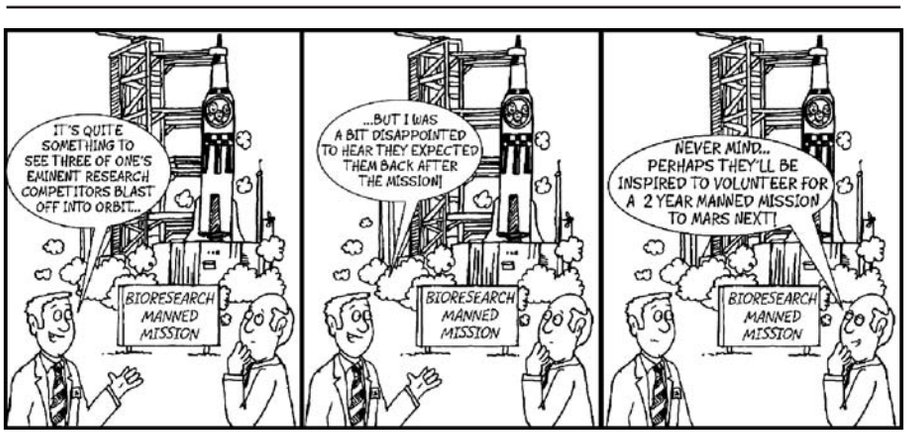
Modern techniques for discovering alterations of gene expression using gene chip technology and proteomics are more likely to succeed if studies are done on astronauts before and after a relatively short duration trip to, say, the International Space Station than by studying relatively large numbers of people for relatively long periods of time lying in beds in Toulouse or Cologne, where the current long and short term bed rest studies have been conducted.

But why should Britain be involved? The answer to this is that we have a long tradition of high quality human physiology (not that human physiology is the only consideration – there are many studies to be done in tissue culture in space which would be invaluable for understanding angiogenesis, osteogenesis, stem cell physiology, etc.). In particular there are a number of physiologists interested in sarcopenia and osteopenia and the biomechanics of the musculoskeletal system, such as Geoffrey Goldspink and Steve Harrridge at University College London, Marco Narici at the Manchester Metropolitan University and at Nottingham my colleague Paul Greenhaff and myself who together possess a portfolio of tools which in its breadth has great potential for understanding the changes which occur with zero gravity. Such expertise is probably unmatched in Europe. If we could gain access to astronauts spending some time on the International Space Station, possibly as part of their training for Aurora, I suggest that, using modern, molecular biological and genetic techniques, we could rapidly discover the nature of the gravity sensor. Having done so, the pay-off would be enormous in terms of identification of pharmacological targets for drug ligands which could stimulate bone and muscle growth *here on earth*. We already have seen a huge expansion in the proportion of our population over 65, and this proportion will grow exponentially, because of the problems of inappropriate lifestyle. Many of these people will suffer muscle and bone wasting for which there are currently no good effective, affordable drugs. Furthermore, there are no good animal models of sarcopenia and osteopenia, so human pathophysiological research is really the only game in town. Although the remits of the BBSRC and the MRC are so tightly drawn as to exclude the funding of human physiological research using space as a tool, it seems to those of us who are concerned about this that were some new government money to be found for Aurora (PPARC are seeking £25 million), and if part were earmarked for human space biology, as it ought to be, it would be best administered through the MRC and the BBSRC, who I am sure would be very happy to do the job.

Of course, another major reason why many of us believe passionately in human space physiology is that it is such a sexy subject. There can be few schoolchildren or university students who would not be very interested in the biomedical problems of muscle and bone wasting in space. We need a flagship project in Britain to re-invigorate the interest of our youth in science. What better than Aurora? And what better than British involvement in Aurora? Why not a British scientist like Kevin Fong, an astrophysicist-turned doctor at University College London, who has done much to promote the idea of a British involvement in space, as Britain's first space physician?

Michael J Rennie
School of Biomedical Sciences, University of Nottingham, Derby

*http://www.star.ucl.ac.uk/~iac/AG_Moon_Mars.pdf



The Journal of Physiology

The Editorial Board meeting held in April was one of the largest ever, with 35 Editors attending. It was the first meeting for Richard Fitzpatrick (he eventually made his first meeting after a couple of earlier attempts) and Caryl Hill, new Editors from the antipodes.

As usual, there was much discussion about how to get *The Journal's* impact factor over the magic number of 5. There are no easy answers to this apart from only accepting the best papers, which hopefully will be well cited. Perhaps we should do as one journal was rumoured to do, i.e. insist that all authors include an extra reference to a *Journal* paper, or maybe not.

The Journal has recently trialed a press release system through the new publisher. This resulted in an article in *New Scientist* and two other online journals. With the success of this first attempt we are enthusiastic to spot more potential papers.

The Board briefly discussed the publishing of Meetings abstracts as part of *The Journal*. Over the lifetime of *The Journal*, these abstracts have been published as part of a normal volume but it was in 1991 that they were first published as separate Proceedings issues. Since January 2003 they are only published online on the Society web site. There are mixed feelings about whether they should continue to be part of *The Journal* and I am sure this will be discussed by Members before any decision will be made.

It was useful having Liz Marchant from Blackwell at the meeting, who is the main contact now for both journals. She informed us that 63% of our 2003 subscribers had taken out a subscription this year, which is apparently a perfectly acceptable percentage for this time of the year.

We were saddened to hear of the death of two ex-Editors, Tony Edwards (who also served as Press Secretary and Chairman) and Hirosi Kuriyama.

Jill Berriman

William Large (above) has been appointed as Chair-Elect to take over from Stewart Sage as Chair of the Editorial Board of *The Journal of Physiology* in July 2005.

Caroline Rae (left) and Melanie Parkin pictured at their 'farewell' meal with staff from the Publications Office at Brown's restaurant in Cambridge

Publications Office

At the end of February the Publications Office said a sad farewell to Melanie Parkin and Caroline Rae (pictured above), who had worked as Distribution Assistants for 6 years and 3 years respectively. The Bench>Press manuscript submission database, introduced by *The Journal* in November 2001, has streamlined the handling of manuscripts to the point where there was insufficient work to justify the employment of four staff in the Distribution Office. Melanie and Caroline therefore accepted the Society's offer of voluntary redundancy in the hope of pursuing more demanding positions elsewhere. Dave Gunn left in May. Based in the Cambridge office, Dave has been responsible for IT since joining the Society in 1996. Our very best wishes for a happy future go with all three of them.

The Journal of Physiology Symposium

A Symposium in honour of the late Eberhard H Buhl will take place on Friday, 10 September 2004 at the University of Leeds, Leeds, UK. Entitled 'Structure/function correlates in neurons and networks', speakers will include:

Brian Robertson (*The Journal of Physiology* Editorial Board)
Peter Somogyi (Oxford, UK)
Vincenzo Crunelli (Cardiff, Wales, UK)
Ole Paulson (Oxford, UK)
John O'Keefe (London, UK)
Hannah Monyer (Heidelberg, Germany)
Roger D Traub (Brooklyn, NY, USA)
Istvan Mody (Los Angeles, CA, USA)
Katalyn Halasy (Budapest, Hungary)
Gianmaria Maccaferri (Chicago, IL, USA)
Gabor Tamas (Szeged, Hungary)
Ivan Soltesz (Irvine, CA, USA)
Alex Thomson (London, UK)
Kai Kaila (Helsinki, Finland)
Stuart Cobb (Glasgow, Scotland, UK)
André Fisahn (Stockholm, Sweden)
Roland Jones (Bristol, UK)
Miles A Whittington (Leeds, UK)

Full details are available at http://www.jphysiol.org

Eberhard Buhl's work will be celebrated at *The Journal of Physiology* symposium in his honour at the University of Leeds. Untilf his untimely death last year at the age of just 43, Eberhard was Head of the School of Biomedical Sciences at Leeds and his research attracted major research grants totalling over £2 million, from sources such as the MRC, the Wellcome Trust, German medical research charities and the National Institutes of Health in the USA.

Eberhard (pictured above) was a member of *The Journal's* Editorial Board from 2001-2003 and in 2002 was appointed to membership of the Neuroscience Board of the MRC.

UK grad courses

Don't put off that course, advises Laura Blackburn – it may be a pleasant surprise!

Laura Blackburn

There is a great deal of emphasis on the wide range of skills needed by research scientists today. Knowing which transferable skills are important and relevant can sometimes leave you feeling a bit bewildered. Courses run by the UK Grad Programme, which are highly recommended by the research councils, are a good place to start, but deciding which one to go on can in itself be rather daunting. I have to admit that I am guilty of putting it off for as long as possible. I had visions of being stuck on a windy hillside in the Lake District with an unknown group of people, trying to make a raft with two fairy liquid bottles and a ball of string that would get us home down the rapids to safety, and all in the name of self improvement!

The truth was less dramatic and a pleasant surprise. I opted for a 2 day non-residential course closer to home, which was useful for my PhD and taught me a few things about myself which I didn't know (and confirmed many things that I did!). The emphasis was on team working, discovering how you interact as an individual with other people, and also how you form a part of the team as a whole.

After some very brief introductions we were launched into the exercises. The first was to design, build and market a gadget that could solve a world problem. This was an opportunity to be innovative and imaginative, aided by the contents of an envelope containing the Blue Peter basics – string, paper, tape, plastic cups and coat hangers.

We then moved on to a case study, looking at an environmental problem and how it could be solved. Each group represented a different party involved in the crisis, and it quickly became clear how difficult it can be to sort out problems on a large scale, especially when people's livelihoods are involved.

I found the most intriguing part of the course filling in questionnaires that looked at personality types and team roles. It was interesting to see how different types interact and how understanding these differences makes interacting with people you might not get on with easier.

We also had sessions on ways to plan your time and work, and on dealing with any problems that arise in the course of research. Most importantly, I met other research students and found that, unsurprisingly, everyone has difficulties at some point but the vast majority can be easily solved.

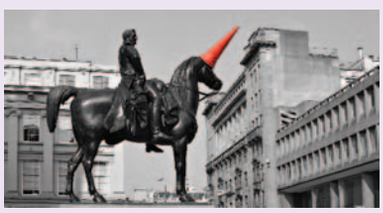
There are longer residential courses on offer, with a wide range of training, which may even involve a touch of raft building! Funding is available from the research councils, so if you were not sure about attending a course, maybe you could give one a try. Information is available at: http://www.grad.ac.uk.

Laura Blackburn
Department of Zoology, University of Cambridge

Thanks to those of you that voted for a new Affiliate representative. I am please to announce that Patricia de Winter will replace Catherine Bleasedale. She is a mature student at Birkbeck, University of London, and about to complete her PhD. She has been an Affiliate Member for 3 years and is keen to promote the involvement of young physiologists in shaping the Society's future. When Rob Wykes, the other Affiliate representative, steps down this September Helen Taylor will take his place. Helen is a PhD student at Sheffield, and will work to improve communication with Society Affiliates.

Affiliate Members – don't forget to send in your contributions for* Physiology News *to Laura at lmlb2@cam.ac.uk

Glasgow: art and culture



(*Photographs by Prem Kumar*)

See p. 40 for Glasgow personalities

What's new in anaesthesia

Dear Editor,

While Bill Winlow's description of the use of neuromuscular blockers in anaesthesia (*Physiology News*, **54**, 11) would have interested your readers as physiologists, as potential patients it must have been rather alarming. Fortunately, much of what he said bears little relation to clinical practice. Postoperative residual curarisation (PORC) was a major problem with the traditional long acting non-depolarising muscle relaxants (d-tubocurarine, alcuronium, pancuronium – all of them excreted in the urine) particularly in patients with impaired renal function. With their slow offset one could not attempt to reverse them (with neostigmine) for at least 40-50 minutes after administration. To do so led to only partial recovery of neuromuscular function and impaired movement and ventilation. Postoperative residual curarisation is not a problem with the modern neuromuscular blockers (vecuronium, atracurium and mivacurium). They have much shorter durations of action, can be easily reversed within 30 minutes of administration and have a far more rapid offset, so it is not always necessary to reverse their action with neostigmine. These drugs are also metabolised in the blood stream (atracurium, mivacurium) or in the liver/excreted in the bile (vecuronium) so renal function is not a major consideration.

Most of us do not rely on subjective assessments of muscle strength (head lift, hand grip etc) to assess recovery but monitor neuromuscular function using a nerve stimulator. The 'train of four' is a research technique for those interested in these drugs, but is almost impossible to use properly in routine clinical practice. It is possible to observe the 'train of four' or test its strength manually, but four brisk and apparently equal responses can still denote only a partial return of neuromuscular transmission. To wake a patient up in these circumstances without giving neostigmine may well result in inadequate ventilation and it could be that this is what Bill Winlow is referring to. More predictable is the motor response to a tetanic stimulus; a strong sustained contraction with no evidence of 'fade' denotes full return of neuromuscular transmission – not exactly a new observation!

While it is nice to have the advances in one's trade described in the Society's publications I was somewhat alarmed by Bill Winlow's interpretations. Should any of our Members go into hospital for surgery they can be assured that under anaesthesia all their physiological functions will be monitored properly and they will not be woken up until they can breathe adequately. I would not like them to think they were at the mercy of a bunch of pharmacological cowboys.

Iain Campbell
Department of Anaesthesia, Wythenshawe Hospital, Manchester, UK

Bill Winlow replies:

I agree with much of what Iain Campbell says and I very much hope that I have not unduly alarmed any fellow physiologists who might be contemplating surgery in the near future. However, I feel that I must address some of his comments. Before doing that, let me make my own position clear. I am a medical writer and as part of my job I am managing editor of *aspects* in *anesthesia*, which has an independent editorial board and is supported by an unrestricted educational grant from Organon.

There is still clearly an issue relating to post-operative residual curarization amongst anaesthetists, and serious worries about antagonism of neuromuscular blockade and reversal of the effects of neuromuscular blocking agents (NMBAs). These were topics that were discussed in both the European and American societies of anaesthesiologists in 2003. I note that the issues are again being raised this year in a number of sessions in both the World Congress of Anaesthesiologists in Paris in April and at the European Society in Lisbon in June. Much of the discussion centres on restoration of voluntary control of the airway after surgery, as I made clear in my original article.

The questions relating to reversal of NMBAs are seen as very important by a number of leading academic anaesthetists on both sides of the Atlantic. In addition, several drug companies (without whom anaesthesia would not be possible in the first place) have invested substantially in trying to develop rapid offset NMBAs or binding agents that rapidly reverse neuromuscular blockage. Of course, development of such drugs would also help to increase the efficiency of surgeons, anaesthetists and nursing staff, because patients would have to spend less time in the recovery room following anaesthesia. There is therefore a clear economic argument in favour of such drugs, but only if they do not harm the patient.

With regard to Dr Campbell's thoughts on the 'train of four' ratio, I gather that this is still used more commonly than tetanic stimulation in the UK. I do agree with him that not giving a patient neostigmine could result in inadequate ventilation. However, if a compound was available that could reverse the effects of NMBAs more rapidly and with no side effects, wouldn't that be well worth having in the pharmacological armamentarium?

Bill Winlow
Medical Writer, Prime Medica Ltd, Knutsford, Cheshire

'Emeritus' membership?

Dear Editor,

I am long retired and unable to get to meetings readily, but I still much value my (reduced-rate) membership of the Society, reading *Physiology News* with pleasure and interest, and at least scanning the Meeting programmes. I'm happy with the present system – though not all might feel able to afford the subscription – but I'd urge caution in adopting the word 'Emeritus' (*Physiology News*, **54**, 33). When I retired from a Professorship at Cardiff the word was added to my title, and at first I supposed it indicated some special, albeit modest, worthiness. However, I see from the dictionary that it merely meant that I had duly served my time. As it comes from the past participle of emereri and is 'not

naturalized', you would need to alter the ending as appropriate for the feminine or plural forms, which might be a nuisance.

Vernon R Pickles
65 Yarnells Hill, Oxford, UK

On retirement

Dear Editor,
When I retired in 1980, I had just turned 60 and could have remained in employment at Otago University for another 5 years as Professor of Pharmacology. However, that did not appeal to me because I had found that being departmental head gave me too little time for research. I therefore became a student again, proceeding first to a BA and then to an MA in philosophy.

One source of my interest in philosophy was Karl Popper, who taught in New Zealand during the 1940s and who had been brought down from Canterbury to give a course of lectures at Otago. Incidentally, these so impressed Jack Eccles, the Professor of Physiology, that he became one of Popper's first influential advocates. It dawned on me that philosophy was a field in which I could work without needing any equipment, research assistance or even an office at the University. Thanks to the development of such instruments as the word processor and the laser printer, I am now home-based, though I still attend relevant sessions at the University.

Another inducement was realizing that some of my special knowledge could be put to use. For instance, much that has been written about 'the philosophy of science' deals largely with the physical sciences. Relatively little attention has been given to the complex multilevel explanations that are so much a feature of physiology. However, that situation is changing with the realization that progress in the field of 'philosophy of mind' is likely to depend partly upon the study of interacting hierarchical systems.

After I had completed my academic studies, I became especially interested in what is now called 'bioethics'. Some of the chief problems in this field are ones in which I had already become involved as a pharmacologist, e.g. therapeutic trials, drug abuse. My training in philosophy has given me a broader view of these problems than I had earlier, one result being a booklet entitled *Drugs and the Law in New Zealand*.

My chief reason for mentioning these personal details is to indicate that colleagues approaching retirement from a university are likely to have a wider range of choices than between merely easing off and becoming a 'social scientist' (as described so delightfully by Vivian Abrahams (*Physiology News*, **54**, 33) and getting into something so radically different that little use can be made of one's existing expertise.

When I first considered changing the direction of my studies, I assumed from national statistics that I would have to do this by age 60 if I was to expect having at least another good 10 years. Expectation of life has since improved to the extent that someone who retires wholly at 65 may be in for a long, dull future.

Fred Fastier
Emeritus Professor of Pharmacology
University of Otago, Dunedin, New Zealand

Whither physiology?

Dear Editor,
The debate about physiology in modern science has been opened up somewhat dramatically by the startling images in the last magazine of the empty space created by the demolition of the building once housing the Department of Physiology in Birmingham. The letter from Olga Hudlicka (*Physiology News*, 54, p 40) came as somewhat of a surprise to me, although I welcome it since, as the recent former holder of the Bowman Chair of Physiology and Head of the Department, I had been fighting long and hard to retain physiology as an identifiable discipline. Professor Hudlicka's article makes some good points and has an important message. Before dealing with these I feel it necessary to provide a little bit of the recent history of events.

Some 7 years ago the University decided to do away with departments and set up divisions within the various schools that are now part of super-faculties. So physiology was not alone in losing its department status. However, instead of being moved *en bloc* into a division of basic medical sciences or life sciences, as I had strongly argued, physiology was divided up, with the bulk of individuals being placed in medical sciences (with medicine, surgery, anaesthetics, geriatrics and cardiology) and the rest in a division of neuroscience (which included pharmacology, neurology, neurosurgery and psychiatry). Thus, to use Austin Elliott's description, we were 'atomized'. The rationale for doing this was, and still is, unclear, particularly when you know that several of us might be considered as neuroscientists as well as cardiovascular scientists. So where would our natural place be? We thought of ourselves as physiologists and being in one location meant we could interact with like minded scientists. The apparent sidelining of physiology was further emphasised by the unwillingness to recruit new high calibre scientific staff to replace some distinguished colleagues, despite my vigorous requests. However, it appears that things are changing, since somewhat surprisingly, and out of the blue, some 6 months after my departure the Dean has announced he has



Glasgow personalities
From far left: Jeremy Ward, Chris Fry and colleagues; Susan Wray and Society Meetings Secretary Bridget Lumb; Hans Hultborn and Alan North

appointed Janice Marshall to the Headship of the Department of Physiology. Janice is well qualified for the post, and I wish her well in what will be a very difficult task. So things may be changing, although the department is greatly downsized, now less than 50 per cent the size it was in 1997, with the remaining staff scattered throughout the very large medical school building. Is this then a retreat from the original objective since we seem to have come full circle? In a way it is, because it is the beginning of a recognition that physiology is important as a subject in its own right. So let's consider why this should be.

The study of how living systems work is a crucial part of biology and is as fundamental as physics, chemistry and mathematics in understanding the natural world. Hence there are various types of physiologist: plant, invertebrate, comparative, sport and exercise, etc. as well as physiologists in the medical sciences. These exist as strong research groups or even as departments in some universities, and in all cases a critical mass is essential to prosecute the research at the highest international level. This is true in medical schools as well, but here there are further critical factors that argue for a clear identity (probably as a department). A good grasp of physiology is essential for practitioners in the health sciences, including medicine. It provides a way of thinking about biological systems in the context of disease and furthermore ensures a thorough understanding of the basic principles for the best practice of the profession. Therefore those who teach should have a broad understanding of the subject even though their research expertise is in a tiny portion of it. Too often I come across complaints that new staff recruited for their research to enhance RAE scores have little knowledge of the physiology (or for that matter anatomy, biochemistry and pharmacology) outside their research area, yet they are expected to supervise and tutor in the new-style small group teaching. I wonder how much misinformation is imparted which has to be undone later. In general, the old style structure of departments of basic disciplines avoided this. So why change? It is still not clear to me what advantages have been gained by amalgamation. Has it really been driven by Research Assessment Exercise? The reorganisation in Birmingham was not, since the basic scientists in the Division of Neuroscience (mainly pharmacologists and physiologists) were returned as part of the RAE with several of the physiologists from the Division of Medical Science.

Has amalgamation resulted in new collaborations? It is probably too early to know, but my own experience here in Birmingham is that very active collaboration was already occurring with other departments and this was not reflected in the restructuring. For example, my own research involved scientists from cardiovascular medicine, pharmacology, biochemistry and sport and exercise science. Apart from the first of these the others are all in different divisions or schools. So we work with whom we will, not because we are close neighbours. The department gave us the feeling of belonging to something where our voice could be heard and a sense of common purpose. The way we went about our work, the way we thought was as physiologists, not pharmacologists or biochemists, etc. To me there is a clear difference. We need the opportunity to talk with physiologists as part of our home department, but to also ensure that 'over the fence' interaction with our colleagues in other disciplines is made easy. So am I arguing for maintaining the *status quo*? Not really. I am happy with conglomerates of departments providing identity of disciplines is maintained. I can understand that university managers consider the larger groupings more financially viable, but don't let us be deceived into believing it leads to better research or to stimulating the acquisition of new skills. The proven way of doing the latter is via the grant-giving bodies. Our projects won't get funded unless we move with the times.

So I make a plea for retaining departments that represent fundamental disciplines like physiology even though they may be within a conglomerate. They are much more able to respond to new developments because they retain a mixture of expertise. For example, the trend to appoint molecular biologists and cell signallers is leading to a worrying loss of skills in integrative and systems physiology. It is the latter we need to exploit the great discoveries of the genomic era.

John Coote
University of Birmingham

Determinants of human exercise performance

Dear Editor,
Much has been written about the post genomic era. The reality is that we are only just beginning to understand how to integrate genomic datasets with physiologically relevant measures. In recent editions of *Physiology News* (53, p 7; 54, p 8), the functional limitations and adaptability of skeletal muscle have been discussed in separate articles.

From the society's point of view this is unquestionably an important topic as it impacts on disease burden, government economics (from sick-pay to tax revenue from betting on sport) and on the aspirations of individuals (athletic performance). The question is how much do we really know about the determinants of human performance? You can't look at a group of athletes and pick the best by eye, you can't even analyse the style of an athlete and define the likelihood of success (consider the atypical running styles of Michael Johnson or Paula Radcliffe).

It would be easy to presume that performance determinants for achieving a gold medal at the 200 m track event represent an extrapolation from the requirements for catching a departing bus, when you are 'running' late for work. Certainly, they both require a degree of muscular strength and power, likewise they also require a finite level of commitment and motivation (how much do you want that medal or how much do you really want to catch the bus to work?).

The truth is that the majority of detailed scientific studies of skeletal muscle performance are more likely to have

been carried out in the group of 'bus-catchers' than potential Olympic medallists. Observations that a high level of endurance performance cannot be continued when muscle glycogen stores are depleted (Bergstrom *et al.* 1967) appears a robust observation; however, does the availability of glycogen really determine the gold medallist from the silver medallist in the marathon? Likewise, enhancing muscle phosphocreatine stores would appear to potentiate sprinting performance (Casey *et al.* 1996), for reasons that still remain to be fully explained. Yet do we have clear evidence that first past the post had greater PCr reserves? We also know that under pathophysiological conditions, the route for ATP resynthesis can impact on the rate of muscle fatigue developments (Timmons *et al.* 1997), but is this really the primary limitation in the exercise intolerant patient? The simple answer to these questions is that we do not yet have the evidence to make such specific conclusions.

What assumptions can we therefore rely on? A valid assumption that may determine muscle performance under any circumstance is the concept of adaptability. If one fails to adapt to repeated exposure to muscular work, then no amount of inherited ability will take you to the top of your chosen sport. Likewise, the decline in muscular performance with age or disease may simply reflect a failure to maintain the status quo, due to lack of biological response to daily activity. If we are to understand the basis for muscle adaptability, then a reasonable place to start would be to capture the global genomic response to endurance training. Certainly, this should be relevant for cardiovascular-metabolic disease prevention, physical rehabilitation and aspects of athletic performance.

In a recent study, we examined changes in muscle gene expression following 6 weeks of aerobic cycle training using the Affymetrix gene array platform. At the time of our study we had 66,000 probe sets (segments of genes that will bind to and recognise if that particular gene is expressed in our biological sample) represented on the DNA chip. From the 24 subjects that undertook the supervised training, the top eight subjects (in terms of improved performance and enhanced aerobic capacity) were utilised for the gene array experiments. Approximately 1,000 genes were modulated sufficiently to be detected by the microarray (this is likely to be an incomplete list as there are inherent limitations to such methods). Stringent statistical analysis allowed us to identify ~140 genes most modulated at a level of 1.5 fold up or down regulated. Since the muscle samples were taken 24 hours after the last training session these genes did not reflect the acute response to exercise but rather a 'stably' altered expression level.

Interestingly, the majority of the genes most modulated in the young healthy male volunteers did not relate to classic skeletal muscle processes (such as energy metabolism) but rather reflected the remodelling of the extracellular environment. This would be presumed to facilitate such process as angiogenesis, matrix remodelling and muscle stem cell activation. Indeed, we were able to establish that the continued genomic response to aerobic exercise, in *adapting* human skeletal muscle generated clusters of changes in gene transcripts that went in the opposite direction from changes observed in animal models of skeletal muscle atrophy (Lecker *et al.* 2004) This gave us confidence that we were looking at a genuine and functionally coordinated pattern of gene responses. The next question was to establish if any of the 'groups' of genes reflected processes critical to muscle adaptation.

To address this question, we decided to examine some selected genes in the eight subjects which demonstrated the poorest adaptation to aerobic training. These subjects had been identified because despite undergoing the same relative training load, under supervised conditions, they were 'unable' to demonstrate substantial improvements in aerobic capacity, cardiovascular adaptation or exercise performance. These subjects did not differ at baseline physiological parameters from the high responding group. Much to our surprise the low responder subjects failed to demonstrate a significant modulation of genes related to muscle angiogenesis and cell differentiation. For one example, a gene involved in new blood vessel growth was nine fold up-regulated in our high responder group and unchanged in our low responder group. This data allows us to consider a number of interesting questions. Do the successful athletes represent a subgroup of motivated individuals that are lucky enough to adapt substantially to a training stimulus? Alternatively, and perhaps of greater interest, are people who suffer from frailty, cachexia or metabolic diseases related to muscle, those subjects that are unlucky enough not to respond to everyday physical activity?

It is very clear from our study and the data emerging from other research groups that the determinants of adaptability of human skeletal muscle are complex and still poorly characterised. The observation that failure to adapt to aerobic exercise in a robust fashion is reflected in a failure to activate groups of genes, locally in the muscle tissue, is somewhat surprising given that the overriding dogma would still favour a central limitation to aerobic performance. The results of this study indicate, however, that the real determinants of success during this summer's Olympics may have more to do with how the athlete has responded to years of preparation, than any quantitative physiological process during the event.

James A Timmons[1,2]
Carl Johan Sundberg[2]
[1]Centre for Genomics and Bioinformatics &
[2]Department of Physiology and Pharmacology,
Karolinska Institute, Stockholm, Sweden

References

Bergstrom J, Hermansen L, Hultman E, Saltin B (1967). Diet, muscle glycogen and physical performance. *Acta Physiol Scand* 71, 140-150.

Casey A, Constantin-Teodosiu D, Howell S, Hultman E, Greenhaff PL (1996). Creatine ingestion favorably affects performance and muscle metabolism during maximal exercise in humans. *Am J Physiol* 271, E31-37.

Lecker SH *et al.* (2004). Multiple types of skeletal muscle atrophy involve a common program of changes in gene expression. *FASEB Journal* 18, 39-51.

Timmons JA, Poucher SM, Constantin-Teodosiu D, Macdonald IA, Greenhaff PL (1997) Metabolic responses from rest to steady state determine contractile function in ischemic skeletal muscle. *Am J Physiol* 273, E233-238.

Voices of the Future 2004

Emily Ferenczi and Andrew Murton report on the Royal Society of Chemistry's annual opportunity for young scientists to meet UK politicians

Noon, Monday 22 March, 2004. Over 150 young enthusiastic scientists mingled over salmon sandwiches and Thai prawns at Portcullis House in Westminster. There were undergraduates, PhD students, post-docs; physicists, chemists, medics; Brits, Australians, Americans, Germans… the diversity was striking. Once the preliminary socialising was over, we settled down to the serious purpose of our visit to the House of Commons. *Voices of the Future* is an annual event organised by the Royal Society of Chemistry. It provides young scientists with an opportunity to meet and question UK politicians who are involved in science and technology policy, funding and administration.

We were welcomed by Ian Gibson MP, Chair of the House of Commons Select Committee on Science and Technology. As a scientist himself, his vision is that science will adopt an expanding role in the maintenance of the stable economy of this country over the next 10 years. He encouraged us to engage with the media and with Parliament in order to put science in its rightful place.

The Secretary of State for Education and Skills, Charles Clarke, delivered a clear and encouraging speech, emphasising two main points. Firstly, he believes that an important battle has already been won: raising Government awareness of the need to give greater priority to science education. He feels that this commitment to investment in science education is reflected in the recent budget. Secondly, the battle still to be won is in the implementation of this commitment through changes in the curriculum, encouraging relations between teachers and scientists, capital investment in school infrastructure and the provision of incentives for science teaching.

Emily Ferenczi - encouraged to realise that highly qualified, influential individuals shared her concerns regarding the position of science in society

A panel of seven members of the Select Committee of Science and Technology took our questions regarding the decisions and dilemmas we face as young scientists embarking upon our careers. Despite the diversity of fields and ages represented, several themes of shared concern were prominent. The inadequacy of mathematics and science education in schools was addressed, including the decline in number and quality of school science experiments. The point was also raised that too great an emphasis is put on the *teaching* of facts and knowledge as opposed the process of *thinking* and *learning*. Higher education issues were discussed, such as the debate on tuition fees and the under-representation of women in science at university. Of universal concern were postgraduate issues such as the 'brain drain', where talented young British scientists are drawn away from science in the UK by higher salaries abroad (such as in the USA) or in other career paths.

The afternoon continued with an entertaining and informative address by Lord May, President of the Royal Society. He emphasised that the growing scientific and manufacturing capacity in the developing world has increased the need not only for 'knowledge creation' in the UK through teaching and research, but also the need to exploit this knowledge by carrying it into the market place for 'wealth creation.'

We were introduced to a representative of the Parliamentary Office of Science and Technology. The office provides scientific advice to Parliament and they offer 3 month internships to PhD students in science who have an interest in writing for Parliament. This is an opportunity that Young Affiliate Members of the Physiological Society may want to explore. The day's programme concluded with the opportunity to attend a formal meeting of the Science and Technology Select Committee where we heard evidence from the new Director General for Higher Education, Sir Alan Wilson.

The event opened my eyes to the inner workings of Parliament. It was encouraging to realise that highly qualified, influential individuals share my concerns and those of other young scientists regarding the position of science in our society. It is through events such as these, where the voices of the public can be heard, that important issues in science can be addressed and eventually changes can be made for the better.

Emily Ferenczi
Oxford University Medical School

Parliament is often accused of being out of touch with reality, and this accusation extends into the field of science. In an attempt to dispel this myth, the Government, in association with the Royal Society of Chemistry, hold an annual event entitled *Voices of the Future*.

This year's event was held within the amazingly designed and engineered Portcullis House, Westminster. Over 150 young scientists from a diverse mix of disciplines attended the event.

After a brief welcome by the Chief Executive of the Royal Society of Chemistry, David Giachardi, we were privileged with the company of Charles Clarke MP. After speaking on his main objective, altering the public's perception of science, he opened the floor to questions, which he answered in the usual political fashion.

A short break later and we were introduced to the members of the Select Committee of Science and Technology, chaired by Ian Gibson MP. They answered competently any outstanding

questions that the audience had. With the Committee being formed from the three main political parties, it was quickly evident that there was no hidden agenda in their responses. The members, all of whom have established scientific backgrounds, appeared genuinely concerned at the current state of affairs within science in the UK. The committee reassured the audience that they were aware of the issues, including specifically wages, career progression and stability, and that they were being addressed.

Finally, a speech by Royal Society President, Lord May. It was good to know that the Government is trying to support the international reputation of British led research, and more importantly, the scientists behind it!

Andrew Murton
University of Nottingham

Deputy Executive Secretary on winning team

Maggie Leggett and Louise Archer collect the ATHENA award at a Royal Society reception.

Last year I attended the launch of a Scientific Women's Academic Network ('SWAN') at London Metropolitan University. The audience at the launch suggested that there should be more coordination between these networks and other women in science activities in universities. To this end the manager of the London Metropolitan SWAN, Louise Archer, formed a working party to develop a charter for women in science. Louise and I led this project, which involved significant consultation and redrafting. It became clear that the approach was both novel and welcomed by other stakeholders. We decided to enter it for an ATHENA award, and were asked to present the work at an event held at the Royal Society. I was extremely pleased when we won a prize sponsored by the Institute of Physics, who are very supportive of this work and of women in science issues in general. The prize money will be used to launch and disseminate the Charter. Affiliate Members will be aware that in early April I advertised for some scientists in the early stage of their careers to join the group to help progress the Charter and other women in science activities. I was amazed at the response, with more than 10 Affiliates volunteering in the first 24 hours. We now have a large working party and an even bigger virtual discussion list. I think the level of the response – which was not just from UK based Affiliates – demonstrates the size of the problem. I hope that the Charter will prove to be a useful document, by highlighting the issues, sharing good practice and encouraging Institutions to be more supportive of female researchers.

Maggie Leggett

If you would like to join the women in science virtual discussion list, please email me at mleggett@physoc.org.

BIOSCIENCES FEDERATION

The first few months of 2004 have been an exciting time for the Federation. Those of you who look at the website (www.bsf.ac.uk) will be aware that the letter to the Prime Minister regarding the honours system controversy received a response with a hand written note from Tony Blair saying 'As you know, I am fully supportive of the scientific community on this issue. But I can't help what's in the press!' There is also to be a full enquiry into the honours system, which at time of writing is on-going. Other recent successes include:

Working Party on Sustaining Biosciences in the UK

The recommendation to set up this working party came from the members meeting. As a first step the Federation has invited selected stakeholders to a working dinner. Almost all the invitees accepted, including Derek Burke (Government Advisor), Derek Bell (Association for Science Education), John Coggins (Scottish Education), John Holman (York), Caroline Hurran (Wellcome Trust), Jane Lewis (GSK Academic Liaison Manager), Colin Miles (BBSRC), Michael Reiss (Inst of Education) and the President and Treasurer of the BSF. The willingness of senior figures to become involved is an indication of both the importance of the issue and the respect with which the Federation is held.

European Liaison Group

At the second meeting of the Federation's European Liaison Group in February, which included delegates from the Royal Society, MRC and BBSRC, the Wellcome Trust, the ABPI, Academy of Medical Sciences and medical research charities (the BioIndustry Association has since joined) there was a strong feeling that the case has not yet been made for a European Research Council. The meeting recommended that the biomedical sciences should be lobbying for research to be funded on a European scale only where this adds definite value over national funding.

Other items discussed included the revision of the Directive regulating animal research; implementation of the Clinical Trials Directive in the UK; Commissioner Busquin's call for a European medical research forum: and EU Chemicals policy. Delegates agreed to bring to the next meeting the recommendations of their organisations on priorities for the UK Presidency of the Commission in 2005.

Survey on awareness of a joint Code of Practice for commissioned research

DEFRA, BBSRC, NERC and the Food Standards Agency (FSA) intend to introduce a code of practice for research that they commission from June 2004. In the case of BBSRC and NERC the code will apply only to their research institutes, but for DEFRA and the FSA it will apply to university labs as well. The Federation has published a survey showing that workers in research institutes are well aware of the need for enhanced quality assurance

procedures to be introduced by June, whereas those in university labs are generally ill-informed and unready. The Federation considers that it is unsustainable for there to be different standards of quality audit required for research institutes and university labs, and within university labs for work commissioned by BBSRC and DEFRA, for instance. A report has been sent to the Heads of Quality Audit of the participating research funders, and we await a reply.

Education Committee

An article I wrote based on last October's Education Colloquium was published in the Spring edition of *Science in Parliament*, the Journal of the Parliamentary and Scientific Committee. It appeared alongside articles by the Higher Education Minister Alan Johnson and science curriculum adviser John Holman. The Federation has also recently collaborated with the *Independent* newspaper to produce a supplement on the Biosciences. It is a useful guide to university education and careers in the life sciences.

£20,000 donation from the Research Councils

The MRC has made a one-off donation to the Federation of £10,000, BBSRC £7,000, and NERC £3000, to cover a 3-year period. Colin Blakemore wrote "I have a very high regard for the Federation and its work; much has been achieved since it was formed, and much is promised". The support of the Research Councils is welcomed; this move should pave the way for future collaboration.

Future events

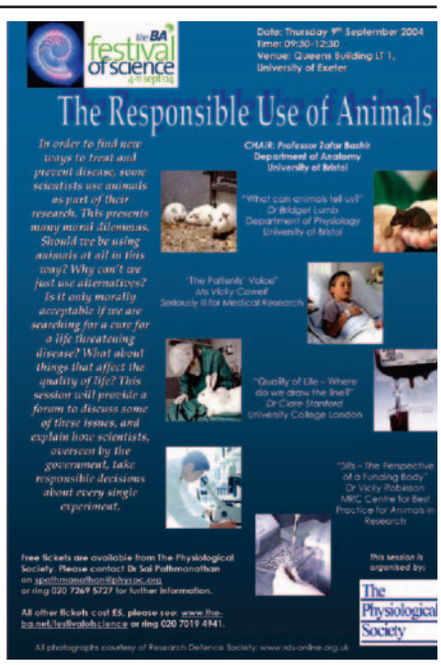
The Federation's workshop at the British Association Festival of Science will be held on 9 September (see separate advertisement). There will be a symposium on the commercialisation of bioscience on 12 October at the Royal Society. There will also be three careers conferences, at King's College London (6 Nov), Leeds University (20 Nov) and Glasgow University (27 Nov).

Maggie Leggett

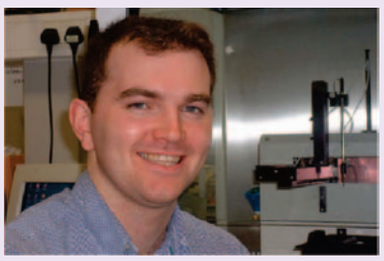
Archives

To complete its set of *Experimental Physiology* (formerly *The Quarterly Journal of Experimental Physiology*) and for archiving purposes, the Publications Office is looking for copies of volumes prior to 1986 (volumes 1-70).

If you have any of these volumes which you no longer need, please contact Emma Ward (eward@physoc.org). Any postage costs involved will be reimbursed.



Pfizer Prizes



Pfizer Prize winner Derek Scott

I was very pleased to receive the Pfizer prize for my oral presentation entitled 'cGMP/PKG II-dependent inhibition of a pH-dependent Zn^{2+}-evoked electrogenic transport pathway in human intestinal Caco-2 epithelia' given at the Society's 2003 Manchester Meeting. This was part of our group's work investigating electrogenic transport processes evoked by iron and zinc in Caco-2 cells, and whether they correlate with changes in metal transporter expression. I have recently taken up a post as Teaching Fellow in Biomedical Sciences at the University of Aberdeen, where I can combine teaching physiology with my research.

Derek Scott
College of Life Sciences and Medicine, University of Aberdeen

Sohag Saleh (above), from St George's Hospital Medical School, also won a Pfizer Prize at the Society's Manchester Meeting for a talk entitled 'The characterisation of voltage dependent currents and calcium activated chloride currents in the mouse portal vein'.

Lauren Mackenzie (above) from the Babraham Institute won the poster prize at the Cambridge Meeting for her poster 'The spatial properties of calcium transients modulate contraction in rat atrial myocytes'.

The truth is out there – but where?

I don't believe it myself. Can I, as a working hospital doctor – and reader of your magazine - pose you physiologists a question:

Do you actually teach medical students physiology these days?

Yes, yes, I do realise that I sound like a cross between Victor Meldrew and a caricature of an old-school consultant surgeon. But is it really too much to ask that the medical students understand at least a few important basic principles of whole body physiology before they are let loose on unsuspecting members of the public - and their colleagues?

Please - at least the principles where ignorance actually can get quite dangerous on occasion.

I am sick and tired of hearing junior doctors tell me: 'This patient with a gastrointestinal bleed is stable after fluid resuscitation' on my ward round. I am then presented with a patient who, having had a litre of 5% dextrose solution intravenously, has a transiently 'normal' blood pressure. No mention of the raging tachycardia, non-existent urine output, and obvious hypovolaemia.

Another example: why do even middle grade doctors stare back at me blankly when I try to explain to them why the inotropic drug Dobutamine tends to lower a patient's blood pressure? β - adrenoreceptors, anyone ? Different types in various bits of the body ?

Is that really too much to ask?

And there is worse to come: respiratory physiology. I believe there is actually a nice little easy-to-read book out on that one. Pocket-sized, even. Unfortunately, few of my junior colleagues seem to realise that simply measuring a patient's peak flow rate is no way of monitoring them for impending respiratory failure due to muscular weakness (as seen, for instance, in Guillain-Barre syndrome). (You have to monitor their vital capacity, which better reflects the overall respiratory 'muscle power'– another of those things physiologists used to teach back in the old days).

Sorry? What's that? It's not the physiologists' fault?

Ah yes – enter Problem Based Learning.

As my physiology colleagues in the university never tire of reminding me, the students teach themselves nowadays, and therefore the 'facilitator' does not actually need to know any human physiology at all.

Indeed, most of the medical students I meet on the wards call PBL 'DIY Medicine' (although I have heard it called much worse).

Personally I think that's exactly where the problem lies.

Just look at those examples above. They are all real situations I have seen, and there are many more, where it is obvious that basic principles of human physiology hadn't been understood.

I am sure my junior colleagues had done their homework as students and had read, copied out, PBL-discussed and even learnt the appropriate chapters in the recommended books. Unfortunately, no one suitably qualified seems to have been around to actually check whether they understood or could apply their knowledge. Don't get me wrong. I do think PBL is a good idea. Well, some of it. It puts knowledge into context, teaches self-motivated learning, etc. etc.

But I do get a sneaking suspicion that the bit where the tutor doesn't have to know much – any? - human physiology is just a bit too convenient in an age where many physiology departments (if they are still called that) appoint and retain staff mainly on the basis of the research money they generate, rather than their ability to teach.

Yes, even the most RAE-ravaged department will still be able to teach (and get the money for teaching) medical students, because a highly research-active yeast cell cycle molecular biologist (to take just one example) can still tutor a medical PBL group.

I don't think so. You see – I believe there is something quietly going seriously wrong here. The way government money is distributed does not provide enough reward for good teaching, which has given the universities the wrong idea. Teaching is neglected - unfortunately with dangerous real-world consequences.

Will this ever change? Possibly. After all, the students - soon to be charged three grand a year up front for their university education - might actually start demanding to be taught.

Now there's a nasty thought. But it might just do your granny a favour if she ever needs to go into hospital.

The author is a harassed doctor working in general medicine

For more on this issue, see the letter from John Coote on p. 39.

Do Society Members think physiologists - or physiology departments - should be responsible for teaching this sort of stuff any more? Or should clinical medicine teach medical students their physiology? **WRITE IN AND TELL US WHAT YOU THINK.**

Gerald A Kerkut

1927 – 2004

Gerald Kerkut would have been successful in whichever profession he chose. He could have been a musician, a banker or studied medicine. In the event he selected reading natural sciences at Cambridge (1945-48), where he proved a first class student, receiving prizes from his college, Pembroke, as a mark of his success. Gerald remained at Cambridge within Zoology for his PhD (1948-51). This was the period when Sir James Gray was Head of Zoology and locomotion was a major research interest of the department. Gerald, selected, or was given, the topic locomotion in starfish, which involved large amounts of cine photography of tube feet movement. Under the guidance of his supervisor, Eric Smith, Gerald set out to determine which of two theories was correct for locomotion in *Asterias rubens*. The choice was either 'traction' theory where the foot extended, attached and then contracted, pulling the animal along, or 'lever' theory where the foot acts as a strut which can be used as a lever to propel the animal along, as a person uses their leg. Gerald demonstrated that, depending on circumstances, the starfish could use both methods (Kerkut, 1953). Interestingly, publishing in the same journal volume are many great names in experimental biology including Ramsay, Fatt, Hoyle, Wiersma, Furshpan, Florey, Needham, Munro Fox, Pilgrim, Edney, Katz, Chapman, Trueman, Mitchison, Swann, Williams, Parry and Knight-Jones, most of whom were linked with Cambridge zoology.

Having completed his PhD, Gerald never returned to echinoderms. Instead, with George Hughes, he began work on electrical activity in slug ganglia in relation to osmotic strength. He extended these studies with Brian Taylor following his appointment to a lectureship in physiology and biochemistry at Southampton, the institution where he was to remain for the rest of his academic life. With Kenneth Munday, Gerald helped to establish the Department of Physiology and Biochemistry at Southampton in 1959. This played an important part in the foundation of the Medical School at Southampton with its first intake of students in 1971. From 1956 until his retirement Gerald played a key role in the training of science undergraduates in physiology, biochemistry, pharmacology and related areas. In 1966 Gerald became the second Professor of Physiology and Biochemistry at Southampton and later served as Dean of Science, Chairman of the School of Biochemical and Physiological Sciences and Head of the Department of Neurophysiology. In terms of research Gerald decided that slugs were not the ideal gastropod for research. There were many species which were often difficult to identify and so he looked for an alternative animal. He had been interested in the work of Arvanitaki and Chalazonitis (1955) who had been recording from giant neurones in *Aplysia*. Gerald could see a future in a simple model nervous system where he could study the basic properties of neurones and synapses. However, he decided *Aplysia* was too difficult to obtain and too expensive to use routinely in Southampton. He selected another gastropod mollusc, the garden snail, *Helix aspersa*, and so began a programme of research using this and other model nervous systems which was to extend over the next 40 years.

Gerald had a first class knowledge of the scientific literature and during his first 12 years at Southampton applied this knowledge to a number of fundamental topics. An observation that cockroaches move faster when the vessel they are in is cooled led him to establish the metabolic role of the sodium pump in the generation of the resting membrane potential (reviewed by Kerkut &York, 1971). Gerald enjoyed challenging accepted dogma and this is beautifully illustrated in his inaugural lecture, *The Missing Pieces*, delivered in 1968 (Kerkut, 1969). Gerald and Robert Meech developed an electrode which measured intracellular chloride concentrations. Using identified snail neurones which were either excited or inhibited by acetylcholine, they demonstrated that these two types of neurone contained different concentrations of chloride, showing that the ionic content of neurones could vary.

Gerald also pioneered the idea that amino acids, viz glutamic acid, GABA and glycine, could act as transmitters. He selected various invertebrate nerve-muscle preparations, where acetylcholine was not the transmitter, to demonstrate the release of glutamate under experimental conditions. This complemented the elegant work of the Takeuchis (Takeuchi & Takeuchi 1964). He was also very interested in the transport along axons and provided evidence for fast transport of material down the axon and slow transport in the opposite direction. During this period there was controversy over whether insect neurone cell bodies could generate overshooting action potentials. With Robert Pitman, Gerald demonstrated that at least some insect neurones, the DUM cells, were capable of generating action potentials.

After working for almost 30 years on invertebrate models Gerald turned his

attention to isolated mammalian CNS preparations and with Jeffrey Bagust developed an isolated spinal cord preparation using 3-6 week old hamsters, mice and rats. Using the isolated cord, Gerald investigated the synaptic and non-synaptic components of dorsal horn field potentials. He was particularly interested in the sensory connections within the cord. While listing the advantages of in vitro preparations Gerald always acknowledged that one had to relate such findings to the intact living animal (Kerkut, 1989).This review was the opening chapter of a Festchrift held in Gerald's honour in 1988 and attended by many of his former postgraduates.

Gerald will always be remembered for his record in the world of publishing, both in terms of journals and books. He always encouraged young scientists to publish and often assisted them by publishing their work in one of his journals. Early in his career he accepted the challenge to revise 'BEPS' (Borradaile, Eastham, Potts & Saunders, The Invertebrata) which appeared in 1958. He revised almost the entire text himself, an indication of his breadth of knowledge of the animal phyla. He simplified many of the figures, making them much more student friendly. This approach to teaching was also reflected in the quality of his lectures to students. It was always a pleasure to attend one of Gerald's lectures, even at 9.00 am.

Evolution was another topic which always intrigued Gerald and in his book *The Implications of Evolution*, Gerald critically reviews basic assumptions and implications regarding the origins of life and the inter-relationships of the invertebrates (Kerkut, 1960). This book was one of a series of 55 volumes which Gerald edited on topics in pure and applied biology – zoology. For a period Gerald also had his own publishing company, *Scientechnica*. However, in terms of scientific journal editing, his two greatest contributions were *Comparative Biochemistry and Physiology*, which he started in 1960, and *Progress in Neurobiology*, which he edited with John Phillis from 1973. *Comparative Biochemistry and Physiology* was undoubtedly the journal Gerald achieved greatest pleasure from and will prove his finest editorial memorial. I remember how excited he was when he came into the laboratory clutching the first number. In the late 1950s Gerald met Robert Maxwell who had founded *Pergamon Press* and the two immediately formed a rapport. Maxwell liked many of Gerald's ideas for the publication of science and agreed to publish a journal on comparative biochemistry and physiology. The deal Gerald made with Maxwell was an excellent example of Gerald's business acumen. Instead of receiving a fee as editor, Gerald received a percentage of the profits from *Comparative Biochemistry and Physiology*. Gerald also had productive industrial links and was involved in the design and development of medical equipment.

In 1997 Gerald established a charitable trust for the support of physiological research at Southampton. He had some interesting thoughts on the allocation of grant income and was always very supportive of staff who failed to gain such income but who continued to do good research which they then published. He was particularly supportive of the training of postgraduate students. The trust will represent another memorial to him.

Gerald was a great advocate of new technologies and edited a book on the role of microcomputers in neuroscience (Kerkut, 1985). In the last few years Gerald became increasingly interested in his web site (with the assistance of Frank Goodwin) and wrote on a wide range of topics, not only in science but in politics, student concerns, money and education. The web site (www.soton.ac.uk/~gk/index.htm) proved amazingly popular, achieving over 60,000 hits per week.

Up until the mid 1970s Gerald regularly took part in scientific meetings, always ready to ask a searching question. To the loss of the scientific community he then largely withdrew from attending meetings but continued to communicate through editorials and reviews in his journals.

During the 1950s and 1960s Gerald supported positive links with scientists from the Soviet Union. In 1967 he attended the first international symposium on the Neurobiology of Invertebrates, held in Hungary and organized by his friend Janos Salanki. The Balaton Limnological Research Institute of the Hungarian Academy of Sciences, Tihany, provided an ideal venue for the interchange of ideas between scientists from 'east' and 'west'.

Gerald enjoyed music, art and travel. He regularly practised on his grand piano and derived great pleasure from listening to music. He had an extensive collection of art books and never lost the pleasure in buying a book, particularly if it was a bargain. In his youth he spent several months studying art in Florence and Venice. Up until 5 or 6 years ago, Gerald travelled widely, particularly in the Americas and the Far East. Gerald enjoyed teaching and interacting with both undergraduates and postgraduates. Many will retain enduring memories of his humour and concerned interest in their welfare. During his active research period he trained over 80 postgraduates, whose success will provide a lasting legacy to his memory. He will be fondly remembered by his many friends and colleagues.

Robert J Walker
University of Southampton

References

Arvanitaki A & Chalazonitis N (1955). Potentiels d'activité du soma neuronique géant (Aplysia). *Arch sci physiol* 9, 115-144.

Borradaile LA, Eastham LES, Potts FA & Saunders JT (1958). In *The Invertebrata*, 3rd edn, ed. Kerkut GA, p 795. Cambridge University Press, Cambridge, UK.

Kerkut GA (1953). The forces exerted by the tube feet of the starfish during locomotion. *J Exp Biol* 30, 575-583.

Kerkut GA (1960). *The Implications of Evolution*, p 174. Pergamon Press, Oxford, UK.

Kerkut GA (1969). *The Missing Pieces*, p 15. University of Southampton, Southampton, UK.

Kerkut GA (1985). Microcomputers; the revolution of our time. In *Microcomputers in the Neurosciences*, ed. Kerkut GA, pp 1-8. Oxford University Press, Oxford, UK.

Kerkut GA (1989). Studying the isolated central nervous system; a report on 35 years: more inquisitive than acquisitive. *Comp Biochem Physiol* 93A, 9-24.

Kerkut GA &York B (1971). *The Electrogenic Sodium Pump*, pp 187. Scientechnica, Bristol, UK.

Takeuchi A & Takeuchi N (1964). The effect on crayfish muscle of iontophoretically applied glutamate. *J Physiol* 170, 296-317.

John Atherton Young

1936 - 2004

John Young, who died on 10 February 2004 after a long illness, was a towering figure in Australian physiology and in global exocrine physiology. After studies in medicine in Brisbane, John travelled to Sydney for doctoral training in renal physiology, followed by post-doctoral studies in Berlin, before returning to Australia in 1966 to a Senior Lectureship in Physiology at Sydney University. Subsequently he was promoted to Professor and Head of Department (in rotation with Liam Burke), before becoming Dean of Medicine in 1989 and then Pro-Vice-Chancellor for Health Sciences in 1996, a post he held until his retirement in April 2003.

Despite the increasing pressure of these demanding posts, he remained committed to physiology research throughout his 40 illustrious years at Sydney University and until the day he finally succumbed to acute myeloid leukaemia. He had continuous NHMRC support from 1962 until retirement, and never had a grant application turned down.

John had a true appreciation of the finer things in life. Given the choice of post-doctoral studies in Berlin and Chapel Hill (and remember this was 1965) he chose Berlin, to study with Karl Ulrich. I suspect the choice was heavily influenced by the presence in West Berlin alone of two opera houses, seven symphony orchestras, 30 theatres and numerous museums (John was not afraid to state that he had never kicked a football in his life). He arrived in Berlin with the expectation of studying urea transport in the loop of Henle, but Karl persuaded him to apply micropuncture techniques to salivary glands. This was a pivotal decision. In December 1965 John presented his data at a Meeting of the Physiological Society held at the London Zoo, where they caught the attention of Arnold Burgen, who sought John's permission to include the data in his keynote paper at an international conference on exocrine secretion in Birmingham, Alabama and also arranged for John to be invited as a plenary speaker. Thus, John's career was launched. Thereafter, he quickly became recognised as an authority on exocrine secretion and the undoubted authority on salivary secretion, which he remained until his dying day, as evidenced by nine ISI-defined citation classics and nearly 5,000 citations in all.

John's original studies on salivary duct function (in Berlin) and micropuncture studies (in Sydney), laid the foundation for understanding salivary glands, while whole gland perfusion studies (some through collaborations with myself and Martin Steward) and electrophysiological and microfluorometric studies (chiefly with David Cook) added greatly to our knowledge of salivary secretory processes.

John also strayed in other secretory organs, including the pancreas where we also enjoyed a fruitful collaboration. The Sydney-Manchester connection led to more than a dozen joint publications, including four papers in *The Journal of Physiology* and many communications to the Society, some given by John during his sabbatical in Manchester (in 1981) and subsequent visits, and these led to his election to the Society in 1982.

John was not only an excellent scientist but a true scholar who enjoyed synthesising work into carefully crafted review articles and a superb monograph on the morphology of salivary glands, written with his anatomical colleague Ernst van Lennep. He was also one of the most generous people I know, someone who gave unsparingly to the countless students he trained and counted it a real pleasure to host wonderful dinners for colleagues around the world.

Maynard Case
University of Manchester

Graham Francis Baker

1947 – 2004

Graham Francis Baker passed away at the beginning of March at the early age of 56, having succumbed to a pancreatic tumour after several months of illness.

Graham was born in 1947 and went to Christ's College, a grammar school in Finchley, and then to Bedford College where, in 1969, he was one of the first men to graduate from this erstwhile women's college in physiology in spite of his severe hearing deficit, which rather cut him off from the cut and thrust of normal conversation. He then went on to work with Wilfred Widdas for a PhD, the completion of which was delayed by the untimely death of his father in 1972, also of pancreatic disease. He completed his PhD in 1974 and worked with me for a period of time at St Thomas's and then with Richard Naftalin at King's College London. In 1981 he was appointed lecturer at Bedford College and after the merger with Royal Holloway he moved to Egham.

A popular and excellent teacher, Graham had a good rapport with the students and was well liked by all. Everyone who knew him remarked on his exceptional kindness and helpfulness to those who asked for his advice. He always dressed elegantly and was well known for wearing either an orchid or rose in his buttonhole.

Graham was a very able experimentalist, well organized and had an excellent knowledge of physiology in general and transport in particular. Although he worked independently on respiratory epithelium he continued working with Wilfred Widdas on human erythrocyte transport systems throughout his career. Graham had great skill in translating Widdas's theoretical ideas into practical experiments using self-built equipment. Professor Widdas freely admitted that it was only through Graham's practical skills that they were able to achieve most of the results in red cell transport.

As Wilfred says one of Graham's main scientific contributions was the discovery of the asymmetric action of 4,6 O-ethylidene-D-glucose in inhibition of glucose transport first presented to the Physiological Society in 1973. He showed that the inside transporter site had a very low affinity, whereas the outside bound the sugar with relatively high affinity. His interest in the asymmetry of the sugar transporter continued long after this - one of the last papers he wrote was with M Kaloyianni in 1998 on the effects of ATP on phloretin affinity.

Richard Naftalin and Graham collaborated in a study of the affinity of the inner face of the glucose transporter. They found that the affinity for glucose was variable depending on how it was measured, high on entry but low on exit. Tony Carruthers who was working with Peter Baker at the time and Graham and Richard working together came up with a neat structural explanation for these findings. They suggested that a vestibule at the inner surface of the transporter was a plausible explanation for the kinetic asymmetry of the transporter. The more recent work on effects of ATP on glucose transport support this explanation.

Graham in latter years developed an interest in transport across the nasal mucosa and from this he evolved a number of techniques for studying the human airways *in vitro*. He developed an interest in the effect of air pollution in the airways mucosa and with this he successfully completed an interesting series of student projects with implications for the understanding of asthma. These projects were cut short by his illness.

As well as his ability as a physiologist, Graham had a great interest in horticulture and for many years enjoyed fresh vegetables and flowers from his three allotments. He won many prizes for his horticultural skills at local competitions and the City of London Flower Show. Graham was a keen orchid grower and also kept bees. He was particularly adept in growing many varieties of apples and he was most pleased when be beat one of the landed gentry at a Royal Horticulture Society Show.

Graham married Petroulla (Petra) in 1986. They had two children, a daughter, Emma (16) and a son, Paul (15).

Malcolm Segal and Richard Naftalin
King's College London

Nachman Ambache

1917 – 2004

Born in Egypt in 1917, Nachman Ambache came to this country in 1929 for education at Peterborough Lodge School, London, Clifton College, Bristol and Trinity College, Cambridge, gaining Major Scholarships and First Class Honours.

In 1939 he returned to Egypt to work in Professor Anrep's department and gain some experience of physiological research. On his return to the UK he took his MA (Cantab) and qualified MRCS, LRCP following completion of his clinical training at the Radcliffe Infirmary, Oxford.

From 1943 to 1946 he became Demonstrator and assistant Lecturer in Pathology and Bacteriology at Guy's Hospital Medical School and, in 1947, Lecturer in Physiology at UCL under Sir Lovatt Evans.

In 1948 he settled on a career in physiology and pharmacology joining the full time staff at the MRC Ophthalmologic Research Unit in Judd Street, and later the MRC External Staff at the Royal College of Surgeons, being promoted to Special Appointments Grade. In 1957 his research into prostaglandins led him into the discovery of irin.

In more relaxed moments he enjoyed making music, for he was an accomplished violinist. In later years he became more interested in the physical character of violins, particularly the famous ones. His garden gave him great joy and he loved to share his discoveries of special plants with his many friends.

He died of heart failure on 3 February, leaving a wife and two children, one of whom is a professional pianist.

Desmond Greaves
Lyminton, Hants

(This obituary is published with permission from the *British Medical Journal* (2004, 328, 960).

Hannelore Pawelzik

1960-2004

Hanna joined my group in the Department of Physiology in 1996, having completed her PhD with Walter Zieglgansberger in Munich and began dual intracellular recordings in hippocampal slices with parallel pharmacology and anatomy. Despite severe illness that resulted in a major operation in 1997 and treatment for the rest of her life, Hanna was an active member of the group and of the Physiology Department at the Royal Free. Her courage, kindness, home made cakes and love of opera will be

remembered for many years. The studies that she performed on the pharmacological profiles of the inhibitory connections made by morphologically identified hippocampal interneurones demonstrated that each class of interneurone acts via a specific sub-class of GABAA receptors. Tragically, having returned to Germany after working with us for 7 years, Hannelore died suddenly last month. The full significance of the work she did will probably not be realised for some time. Her findings are becoming increasingly topical since they link the actions of drugs that alter mood and behavioural state to the functions of specific sub-classes of interneurones.

Alex Thomson
School of Pharmacy
London University

Other Members deceased since our last issue. We hope to carry some full obituaries in a future issue of *Physiology News:*

Anthony E Edwards, Hirosi Kuriyama, D M Lewis and Leon Leonidovich Voronin

The biology of human survival: life and death in extreme environments

Claude A Piantadosi. 2003, Oxford University Press, £24.95, 263 pp.
ISBN 0 19 516501 2

Anyone who has camped overnight in the high mountains knows that one of the small compensations for a cold and cramped night is that you can boil the water for your tea more quickly than usual the next morning. Water boils at a lower temperature at altitude because less energy is needed for water to evaporate as atmospheric pressure falls. For example, at about 14,000 feet water boils at 88ºC. What happens if you keep going up in a balloon or aeroplane? At an altitude of 62,800 feet the atmospheric pressure falls to 47 mmHg and water boils at a temperature that may seem familiar, 37ºC. That is, the fluids in an unprotected human body will boil just from the heat of metabolism. This piece of bad news is known as ebullism: the outer dimensions of the body may suddenly increase and unless the pressure around the body is rapidly normalised, unconsciousness follows within seconds and death soon afterwards. Not really surprising given that the major constituent of the human body is undergoing a physical change of state. This altitude limit is known as the Armstrong line after its discoverer. Interestingly, the air pressure at the Armstrong line is about seven times higher than that on the surface of Mars, which gives some indication of just how vicious the current Martian environment is and how difficult it would be to get humans there and back safely. Even if her oxygen supply was unaffected and she was protected from the cold, an astronaut who suffered a suit depressurisation on the surface of Mars would rapidly boil and die of ebullism.

At a time when many physiologists are worrying about whether their subject still exists (just for the record, I have never been among their number), it is refreshing to come across a book which is completely rooted in classical, integrative, systems-level physiology and which also demonstrates so clearly both how important this approach is for understanding many practical problems of interest, and how much more important work there is to be done at this level, without ever having to trouble one's head about DNA, molecular substitution or single channel currents.

In 20 short chapters, Piantadosi treats us to a masterful survey of the key physiological problems facing humans in extreme environments, from deserts of sand to deserts of snow, from the depths of the ocean to the depths of space. The physiological limits applying to lack of food and water, to hypothermia in air and in water, to heat stress, rapid ascent, hyper- and microgravity are all discussed briefly but clearly, with many fascinating examples. A strength of the book is the author's lucid exposition of the amazingly narrow limits which our basic physiological makeup can withstand and his emphasis on the many behavioural ways in which we strive to overcome these limits – a perfectly legitimate, and indeed vital, aspect of environmental physiology that has often been skated over. The book closes with a topical chapter on weapons of mass destruction and another on human prospects for colonising space, which calmly discusses the many problems alongside ebullism which need not just to be solved, but solved with redundancy and adequate safety margins before this Big Idea has a chance of becoming reality.

One example can suffice to show why integrative physiology will always be necessary to make sense of the mass of data emerging from more restricted studies of individual tissues, cells or membranes. Heatstroke is the unfortunate consequence of our core body temperature rising by more than about 5ºC. The most serious effects are shock and multiple organ failure. Interestingly, these effects are similar to those occurring in the setting of septic shock, which are substantially mediated by the lipopolysaccharides of bacterial endotoxin. It turns out that there is indeed a connection between these two apparently rather different pathologies, since the plasma concentrations of lipopolysaccharides in heatstroke victims show large increases. Why? Normally, bacterial endotoxins are sequestered in the gut by tight junctions between intestinal epithelial cells. But this mucosal barrier breaks down at about 42ºC due to decreased blood flow and direct heat injury to the cells, allowing endotoxin access to the blood stream, with disastrous systemic consequences.

The story of human environmental physiology contains riveting tales of triumph and tragedy in extraordinary circumstances, as well as great science. It is difficult to imagine a more engaging way to interest neophytes in physiology or to restimulate a more general awareness of the importance and intellectual excitement of integrative physiology. Piantadosi's book is a superb primer in the field and deserves a very wide readership.

John A Lee

FORTHCOMING PHYSIOLOGICAL SOCIETY MEETINGS

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

Abstract submissions
Authors should submit their abstracts online. Full instructions will be available on the Society's website (http://www.physoc.org/) from the opening day of the abstract submission period.

2004

Cork: 1-3 September
King's College London: 18-20 December
(Joint Meeting with the Chilean Physiological Society)

Focused meetings
Newcastle upon Tyne: 22-23 July
Nottingham: July
Bristol: 4-5 September
Oxford: 1-3 October

2005

Seville, Spain 10 - 13 February
Sponsored symposia in association with the Spanish and Dutch Physiological Societies

Bristol 20–22 July

IUPS 2005 – 35th CONGRESS OF THE INTERNATIONAL UNION OF PHYSIOLOGICAL SCIENCES

San Diego, CA, USA
31 March–5 April

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

Website: http://www.IUPS2005.org

YOUNG PHYSIOLOGISTS' SYMPOSIA

Channels to Networks
University of Leeds
September 2004
For further information contact Helen Garner
Email: bmshlg@leeds.ac.uk

King's College London
17 December 2004
Joint with the Chilean Physiological Society
Theme free symposium, abstracts on all topics welcome
For further information contact Charlotte Waters (KCL)
Email: charlotte.waters@kcl.ac.uk
or Paola Casanello (Chile)
Email pcasane@med.puc.cl

Further information about these events will be circulated via email and published on the website.

ADVERSE REACTIONS TO DRUGS AND CHEMICALS: STUDIES FROM MOLECULES TO MAN

University of Liverpool, Liverpool, UK
9-10 September, 2004
Joint meeting of the British Pharmacological and Toxicology Societies.

email: meetings@bps.ac.uk
Website: http://www.bps.ac.uk

ION CHANNELS: FROM PHYSIOLOGY TO PATHOLOGY

Universidad de Sevilla
7-9 February, 2005
This International Workshop will focus on the general aspects of ion channel molecular physiology and channelopathies. The meeting is sponsored by the Physiological Society and intended for young scientists from the UK, Spain and Eastern European countries, though participants from other countries are also very welcome. Up to 40 applications will be accepted and preference will be given to applicants who will present a poster. Interested applicants should submit a short cv and register online by 1 September, 2004.

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

THE PHYSIOLOGICAL SOCIETY CHANGE OF ADDRESS

The Physiological Society Administration Office has moved to:

PO Box 11319

London WC1X 8WQ

Noticeboard

Notices for the Autumn 2004 issue of Physiology News should reach the Publications Office by 7 June, 2004 (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
List of Meetings during 2004

UNIVERSITY OF NOTTINGHAM

12-13 July (Focused meeting)

UNIVERSITY OF NEWCASTLE-UPON-TYNE

22-23 July (Thurs-Fri) (Focused meeting)

Opening date for receipt of abstracts	26 April
Closing date for receipt of abstracts	5 May

UNIVERSITY COLLEGE CORK AND ANNUAL GENERAL MEETING

1-3 September (Wed-Fri)

Opening date for receipt of abstracts	7 June
Closing date for receipt of abstracts	16 June

UNIVERSITY OF BRISTOL

4-5 September (Sat-Sun) (Focused meeting)

UNIVERSITY OF OXFORD

1-3 October (Fri-Sun) (Focused meeting)

Opening date for receipt of abstracts	5 July
Closing date for receipt of abstracts	14 July

KING'S COLLEGE LONDON

18-20 December (Sat-Mon)
Joint meeting with the Chilean Physiological Society

Opening date for receipt of abstracts	20 September
Closing date for receipt of abstracts	29 September

LIFE SCIENCE CAREERS

Organised by:

BIOSCIENCES FEDERATION

Details of each event and booking forms will be available on the web:

www.bsf.ac.uk/careers

WHERE DOES YOUR FUTURE LIE?

Are you a life science undergraduate postgraduate student?

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

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

6th November 2004	London
20th November 2004	Leeds
27th November 2004	Glasgow

Programme includes:

- Talks on R&D, science communicatio postgraduate/postdoctoral opportunitie teaching, patent examination and muc more.....
- Making applications
- CV checking service