PHYSIOLOGYNEWS

winter 2005 | number 61

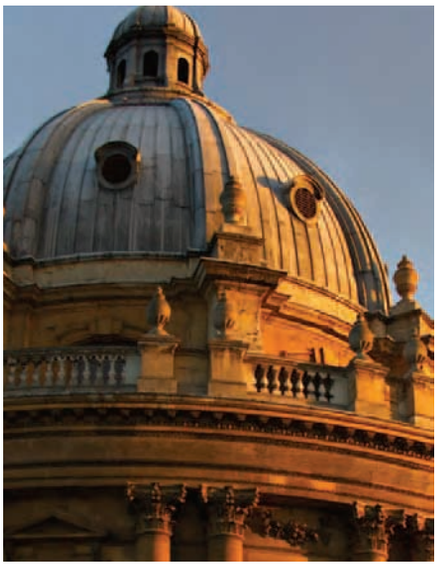
Meetings
UCL
Images of Oxford
Bristol revisited

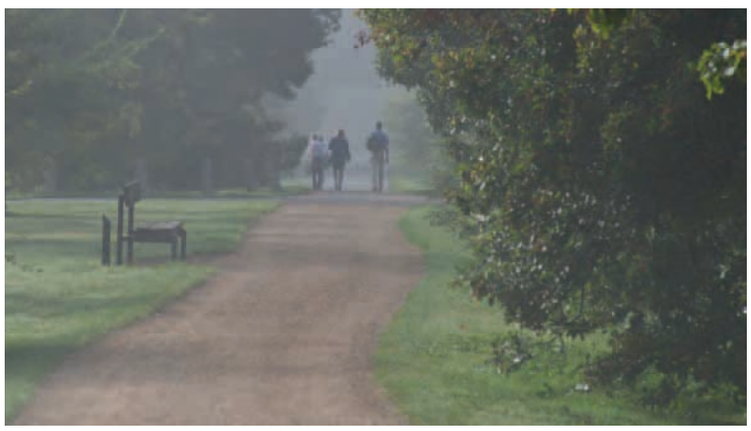
Also featuring:
Physiology in space
Richard Naftalin's 'desert island' selection
Cutting through the melatonin hype
Reflections of a ex-Chair
Letter from Russia
What turned us on to physiology
Winter books special

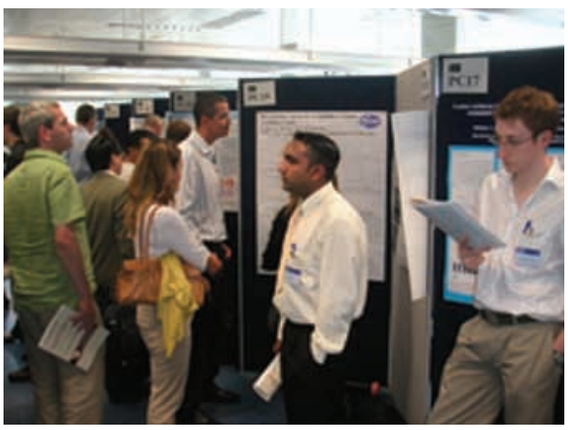
A publication of The Physiological Society

OXFORD FOCUSED MEETING

Ion channels, genes and regulation in smooth muscle
5-7 September 2005







More photos and a report from the Oxford Focused Meeting appear on p. 5

(photos by Prem Kumar and Roger Thomas)

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
P.O. Box 502
Cambridge CB1 0AL
UK

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

See Physiology in the extreme. The case for microgravity research. By Marco Narici and Michael Rennie, p. 19

PHYSIOLOGYNEWS

Action points

Grants

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

Membership applications

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

Change of address

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

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

---

Physiology News

Deadlines

Letters and articles and all other contributions for inclusion in the Spring 2006 issue, No. 62, should reach the Publications Office (lrimmer@physoc.org) by 6 January 2006. Short news items are encouraged and can usually be included as late copy if space permits.

Suggestions for articles

Suggestions for future articles are welcome. Please contact either the 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 the Society's web site: http://www.physoc.org.

Guidelines for contributors

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

Format of articles

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

Length of articles

This will be determined by the subject matter and agreed with the Executive Editor.

Submission of articles

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

Illustrations and authors' photographs

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

References

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

In this issue

This end-of-year *Physiology News* is the largest we have ever produced – 56 pages, up by four pages from our standard 52. We made the decision to publish this 'bumper' edition because of the unusually large amount of excellent material that had arrived in time for the presses to roll.

The watchwords for a magazine like *Physiology News* to aim at are 'interesting', 'informative', 'varied' and 'relevant'. We hope that in the range of content, and the breadth of science covered in the features section, each individual reader will find things that speak to their interests.

One could also add a fifth watchword, namely 'thought-provoking', or even, on occasion, 'controversial'. There is a bit of controversy brewing here and there in this issue, with several pieces containing strong personal opinions. Our hope, as ever, is that these provide food for thought and – even better for a magazine – the starting point for debate. If you agree or disagree with our writers and correspondents, tell us why!

Which brings me to a final point – we can only generate a magazine of the size and quality of Physiology News because you, the readers, supply the copy. Keep it coming, and enjoy your pre-Christmas reading.

Austin Elliott

Viva trauma. Unbelievable! by Mark Cain, p. 51

Currency fraud or just sharp practise?

Reading the scientific journals, and even sometimes the mainstream press, it seems that scientific fraud is on the rise. There have certainly been several ultra-high-profile fraud cases in the last few years, both in physical sciences – notably that of Jan Hendrik Schön of Bell Labs[1] – and in the biomedical sciences (for instance the Herrman and Brach case in Germany[2]). The distinguished physicist and Vice Provost of CalTech David Goodstein, who has written extensively about scientific fraud, has suggested it is much more likely in the biomedical than in the physical sciences because biological variability makes experiments in biology and medicine intrinsically less repeatable and fraud therefore harder to detect[3]. With the exception of the Office of Research Integrity (ORI) in the US, mechanisms for identifying and investigating scientific fraud generally remain patchy and fairly *ad hoc*. In addition, the slow speed of investigation and the modern proliferation of scientific journals, especially in growth fields like biomedicine, can leave workers strongly suspected of fraud by one journal free to publish further suspect work in less sceptical places, or in journals unaware of the suspicions (see e.g. ref 4).

Some commentators argue that the high-profile fraud cases noted above[1-4] are merely the visible tip of a large iceberg of scientific misbehaviour. For instance, in a recent study published in *Nature* in July 2005, one in three of over 3,000 NIH-funded US researchers admitted questionable actions or dubious practises within the last three years.[5] These misbehaviours ranged from falsifying data (rare) to unauthorized use of confidential information (less rare) to altering the design of a study in response to pressure from those funding it (very common).

The results of this survey and recent headline cases notwithstanding, most scientists would like to believe that scientific fraud is rare. In essence, it depends what one calls 'fraud'. David Goodstein distinguishes between what he sees as outright scientific fraud – the invention of data – and what one might loosely call 'scientists behaving badly'. This latter takes in a collection of less-than-ideal behaviours, including misuse of other peoples' ideas short of outright plagiarism, lack of appropriate acknowledgement of co-workers' inputs or of previous literature, and various other means of gaining an unfair advantage. In Goodstein's view, these kinds of behaviour, while clearly substandard, should be distinguished from inventing or grossly manipulating data – true scientific fraud – which he likens to 'counterfeiting the currency of science'. Most of the headline cases of scientific fraud of recent years involve precisely this sort of falsification of data, but in the *Nature* survey only one in three hundred respondents admitted to faking results.[5] The US government currently defines research misconduct as 'fabrication, falsification or plagiarism'[6], broadly reflecting the view propounded by Goodstein.

The counter to Goodstein's moderately reassuring thesis is the 'slippery slope' argument. This view sees the path to perdition – to outright fraud – as starting with small steps. Once one decides it is OK to omit a couple of inconvenient data points that 'must be wrong', or to leave out of a paper the experimental result that does not quite support one's cherished theory, one is on the slippery slope. In the *Nature* survey these kinds of sins of omission were far more common that outright falsification of data – failing to present 'inconvenient' results was admitted by 6%, and dropping observations or data points based on a gut feeling that they were inaccurate was admitted by 1 in 6.

Personally I am surprised these latter two estimates were not larger, given the near-universal need to apply some kind of 'data sifting' in biomedical research. Many physiologists have confronted the problem of trying to differentiate a 'good' from a 'bad' preparation, whether the preparation is a patch, a cell, or something larger. In addition, the small sample numbers typical of experiments on living cells or animals make it hard to use the accepted statistical techniques for objectively identifying erroneous data points or outliers. If five patch-clamp recordings with 'good' cells, good gigaseals, and clear low-noise data give 'result A', while two experiments that produce poorer quality, but still usable, data give 'result B', it is hardly surprising if the experimenter tends to believe result A is the true one. So should the experimenter disregard the two cells giving result B and leave them out of the data analysis? I cannot believe that all physiologists would answer 'No'. So, is leaving out the data from these two cells scientific fraud? This seems a rather harsh judgement. A key point is whether the experimenter remains critically aware of his or her own subjectivity. The question is, of course, where to draw the line. How much of this kind of data sifting can be defended as trying to find the underlying pattern in a chaotic system? When does 'data sifting' become 'falsification'?

Perhaps part of the danger lies in the perceived need nowadays to produce data that is uniformly clear, with everything fitting nicely together and no loose ends, even when papers contain multiple experimental techniques. Some years ago it was fairly common to see, in papers in physiology journals, statements like: 'this result was observed in six out of eight preparations tested. In the other two, a different result was observed, namely …' I have the feeling, admittedly based on no hard evidence, that this has become far less common. In part this may reflect the move to more reduced systems (for instance channels in a membrane patch rather than anaesthetized animals), and the pressure on editorial space, but I suspect the perceived need not to 'confuse' referees and editors plays a part too. The desire to tell a clear story, whether in a paper submitted for publication or in a seminar, means that there is a temptation to leave out the data from the two anomalous preparations in the example above. Or to omit the experimental protocol that produced a result inconsistent with the other eight figures worth of data from one's next submission to *J Physiol*.

What we are dealing with here, at bottom, is the judgement and integrity of individual scientists. Most believe they can tell the difference between omitting points because there was something wrong with the experiment, and omitting them to fiddle the results. An important point here, stressed by former Max Planck Institute director Georg Kreutzberg, is where and how scientists learn good or bad habits of dealing with data. Kreutzberg highlights the role of lab heads and group leaders,[7] as it is they who pass on their habit of integrity, or otherwise, to their PhD students and postdocs. Those trained by data-tweakers, he argues, will go on to be data-tweakers in their turn, with the standard defence, learned from their mentor, of 'cosi fan tutti' – everyone does it.[7] The same goes for other kinds of unprofessional behaviour, which are similarly learned from one's professional role-models.

To close, then, those involved in supervising tomorrow's scientists need to be sure they are passing on good habits. The public remains, on the whole, reasonably trusting of scientists to be professional and objective. They deserve all our help to make sure this trust is not misplaced.

Austin Elliott

1 Dalton R (2002). Nature 420, 728-729.
2 Hagmann M (2000). Science 288, 2106-7.
3 Goodstein D (2002). Academe Jan-Feb 2002. Online at http://www.aaup.org/publications/Academe/2002/02JF/02jfgoo.htm
4 Smith J, Godlee F (2005). *Br Med J* **331**, 245-246.
5 Martinson BC *et al.* (2005). *Nature* **435,** 737-738.
6 See: http://www.ostp.gov/html/001207_3.html
7 Kreutzberg GW (2004). *EMBO Rep.* **5:** 330-332.

Movement neuroscience at UCL

Anybody that has visited UCL in recent times cannot have failed to notice the vast amount of building work that has been going on. At the time of writing (late September), this is still continuing unabated. Fortunately, at least as far as the Medical Sciences building is concerned, it will all be complete by November – just in time for the forthcoming Focused Meeting at UCL on *The neuroscience of human movement in health and disease*.

Of course, many universities have been suffering under major building work as a consequence of the various initiatives to improve their infrastructure. UCL has been and will continue to undergo major changes in other ways too. There have been many mergers in recent years, some of which are still not yet complete. Nevertheless, even bigger changes are planned. The most publicised of these is the impending merger with the National Institute of Medical Research (Mill Hill). Other planned changes are the 'regeneration' programme and the tightening up of student numbers. These changes involve a major shake up of the college involving a reorganisation of 'biomedicine' and, over the next 3 years, 15% reductions in staff (with 5% new appointments in selective areas). The usual cliches about threats and opportunities abound.

Clockwise from above right: Philip Harrison; the main UCL quadrangle; the Institute of Neurology, Queen Square; members of the Department of Physiology relaxing in the Starling Room. Bottom right: UCL Medical Sciences Building.

Are all these changes necessary? Perhaps they are. UCL has grown enormously on an *ad hoc* basis over a long period of time. UCL is certainly one of the biggest HE institutions in the UK with 18,000 students and 3,800 academic and research staff. What does this mean for physiology? Well, physiology is big at UCL. As an indication of this, there are 105 Ordinary Members of The Society at UCL. This is a greater number than at any other single institution and is about 9% of the total number of Ordinary Members in the UK.

Analysis of the distribution of Members at UCL shows that physiologists are scattered throughout the college in many different departments. Of the 105 Ordinary Members, only 31 are in the Department of Physiology, suggesting that more physiology is practised outside the Department of Physiology than in it! This is of no surprise to members of the department, many of whom work closely with members of other departments in UCL. Research into the control of movement is a case in point. There are five Members of The Society in the Department of Physiology studying the control of movement, but twice that number elsewhere at UCL (primarily at the Institute of Neurology). In order to bring these people together the Institute of Movement Neuroscience (IMN) was set up at UCL several years ago. While the greatest number of Members at the IMN are in the Institute of Neurology (Sobell Department of Motor Neuroscience and the Wellcome Department of Cognitive Neurology), Members are drawn from many other departments including the Department of Physiology, the Department of Psychology, the Department of Anatomy and Developmental Biology, the Institute of Cognitive Neuroscience and the Gatsby Computational Neuroscience unit.

In total, the IMN represents the largest conglomerate of movement control scientists in the UK. It is therefore fitting that the first Focused Meeting of The Physiological Society about movement neuroscience should take place at UCL. We look forward to seeing you here on the 19-20 December!

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

Ion channels, genes and regulation in smooth muscle

Smoothies and channelers celebrate Tom Bolton and Alison Brading's inspirational work in the field

Above: Tom Bolton (left) and Alison Brading at The Society dinner. Below: Delegates gather outside the Oxford Department of Pharmacology,, venue for a Physiological Society Meeting at its best

As we gathered on the Sunday evening the heavens opened, but it was only to clear the way for a very special two and half days for the smooth muscle and ion channel fields. The sunshine came out and Oxford was idyllic. By 9 on Monday morning smoothies and channelers packed the lecture theatre and we all had the sense we were to witness a Physiological Society Meeting at its best.

There were speakers and registrants from across the globe – international stars and aspiring young scientists – a sign of fields with a great past and healthy future. There probably wasn't a person in the room who doubted that the high turn-out was a reflection of the very considerable esteem in which we hold Tom Bolton and Alison Brading. This was a chance to show our appreciation and respect for two people who have dedicated their lives to scientific discovery and the greater good of the subject ever since their PhD studies began in the mid-1960s. Tom began in London as a vet, Alison in Bristol as a zoologist, but it was Oxford's Department of Pharmacology that brought them together as they were inspired by the great Edith Bülbring in the late 1960s and early 70s. Alison and Tom have clearly inspired too, ensuring Edith's legacy runs true and rich 35 years on.

Patrick Vallance chaired the first session. Patrick had been taught Pharmacology by Tom during his medical studies at St George's Hospital Medical School and recalled Tom's tough and exacting standards – a characteristic of Tom's we all know and admire. This was obviously a positive experience for Patrick as he went on to an academic position in Tom's department and a Chair at University College London. The first speaker was Mike Kotlikoff (Ithaca, USA) and he got us off to a great start with a talk on 'calcium indicator mice', showing striking images of intracellular calcium measured *in vivo*. This was to set the scene for talks on different aspects of calcium signalling events in smooth muscle – Dima Gordienko (London), Mark Evans (St Andrews), Yuji Imaizumi (Nagoya) and Casey van Breemen (Vancouver). Coupled with this we saw the cutting edge of studies exploring endogenous non-selective (but not completely so!) cationic channels and TRP channels – Sasha Zholos (Kiev), William Large (London), Ryuji Inoue (Fukuoka), Seiichi Komori (Gifu), Chris Benham (GSK, Harlow), Phil Aaronson (London) and Bernd Nilius (Leuven). Bernd showed us fascinating data on TRPV4 and ended his talk exposing the tougher side of science as his *in vivo* studies on the knock-out mouse yielded the opposite result to that expected. Kenton Sanders (Reno) gave the Smooth Muscle SIG Lecture, Diomedes Logothetis (New York) the Ion Channel SIG lecture – showing two extremes, from the origins of rhythmicity in the gut, to the molecular basis of PIP_2 regulation of an array of membrane proteins including channels. The theme of physiological rhythmicity was taken up eloquently by Sue Wray (Liverpool), Mark Hollywood (Dundalk), Hikaru Suzuki (Nagoya) and Tom Bolton. Steffen Hering (Vienna) remembered his early days in Tom's lab and showed us that we still don't understand the mechanism of action of

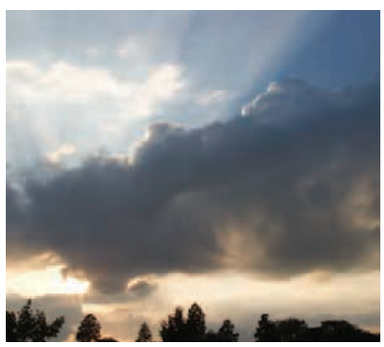
Clockwise from above:
1 Sean Ward (left) and Alexander Zholos
2 Chris Benham
3 David Beech
4 Sunset over Oxford
5 Kenton Sanders
6 Medical teaching block
7 Rick Lang
8 (from left) Sung Joon Kim, Tom Bolton, Seiichi Komori and Toshihiro Unno
9 Steffen Hering
(*Photos by Prem Kumar and Sergey Smirnov*)

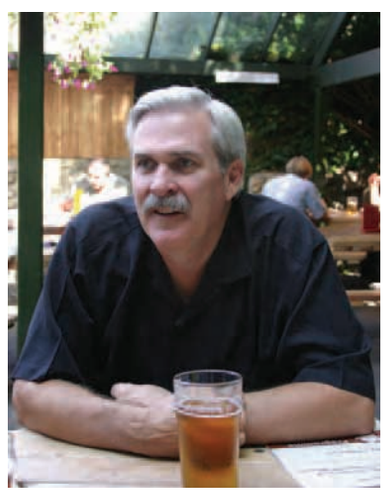
calcium antagonists – despite a huge investment of effort. The Meeting included new insight into transcriptional control mechanisms – Karen Lounsbury (Vermont) and David Beech (Leeds) – and the further complexities and diversity of potassium channels – Rick Lang (Monash), Alison Gurney (Manchester) and Ligia Toro (Los Angeles). There were also vibrant poster sessions throughout the Meeting, with plenty of time for discussion.

The speakers' dinner saw 30 international researchers walking from Lady Margaret Hall – Alison's Hall – along to the river side, its moored punts, and the Cherwell (pronounced Charwell) Boat House restaurant. Windows were open, it was a beautiful evening, Sancere flowed, the food was perfect. The following evening began with a wine reception in the gardens of Lady Margaret Hall followed by a Society dinner of impressive quality. Noel McHale was schedule to give an after-dinner speech on Alison, but a freak cycling accident left his finger severely broken and so he was in hospital in Ireland. Kenton Sanders kindly stood in at the last minute and entertained us with his usual panache and fond memories of times with Alison. Chris Benham reminded us all of Tom's early days and continuing sporting prowess; Tom responded with a defence of his days as a prefect, and warm thanks to the many who had come from near and far to be present, clicking their cameras with the energy of a world media event. Prem Kumar, as in-coming Meetings Secretary, gave his debut speech, giving thanks to attendees, speakers and sponsors, including The Society and the British Heart Foundation.

The third day ended just before lunch as members of Alison's department gathered in the lecture theatre. We were treated to a glimpse into a wonderful mind and recollections of treasured moments in Edith's garden – the origins of so much good in the field. Alison displayed a memorable example of how to inspire, with her intellectual energy, knowledge, and sense of fun. The next generations have a lot to measure up to.

David Beech, Anant Parekh and Phil Aaronson
Meeting Organisers

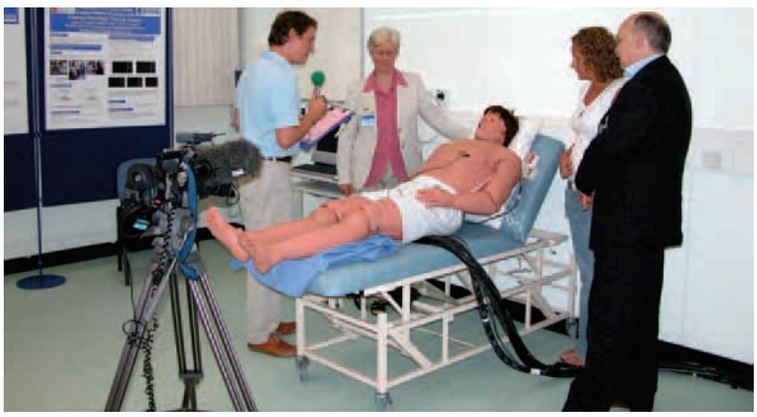




'Stan-power'

Judy Harris looks at computer-controlled patient simulators as novel physiology teaching tools

This summer, the Physiology Department at the University of Bristol welcomed the arrival of Stan – a rather unusual addition to our departmental staff. Stan is a realistic, life-sized high fidelity Human Patient Simulator or manikin and he was unveiled during the Teaching Symposium at the joint meeting of The Physiological Society and Federation of European Physiological Societies in July.



At £125K, Stan didn't come cheap but his potential as an innovative and powerful learning tool is enormous. The manikin is controlled by sophisticated Mac-based software which provides the mathematical modelling for a range of physiological parameters including ECG, arterial and venous blood pressures, cardiac output, rate and depth of breathing, blood gas concentrations and body temperature. Pulses can be palpated at appropriate pressure points (carotid, brachial, radial and pedal) and simulated heart and lung sounds can be monitored with a stethoscope.

We have been able to purchase two of these simulators as part of a £4.5M HEFCE Centre for Excellence in Teaching and Learning (CETL) award to the medical science departments at Bristol. The main remit of the CETL, which is funded for 5 years from April 2005, is to develop initiatives in anatomy, physiology, pharmacology and histology to allow our existing teaching to be integrated with a range of novel models and simulations. An additional theme is to emphasise the importance and clinical relevance of medical sciences for medical, dental and veterinary science students.

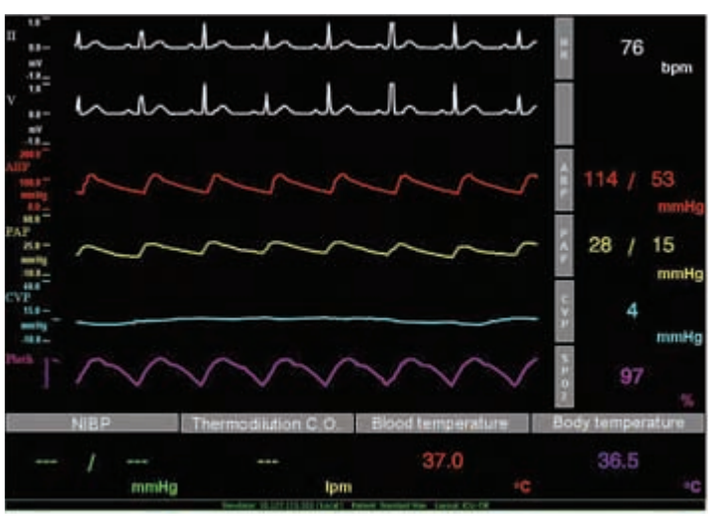
Each of our new simulators is housed in a refurbished, self-contained Human Patient Simulator suite, one associated with our physiology teaching laboratory, the other with pharmacology. Connection of the manikin to compressed air, oxygen, nitrogen and carbon dioxide via a flexible umbilicus enables it to 'breathe'. The compressed air also provides hydraulic energy for the palpable pulses.

Distensible 'lungs' in the chest are connected to external bellows that generate appropriate gas exchange as well as physical excursions of the chest wall – Stan consumes oxygen and generates carbon dioxide at rates that are automatically adjusted for a variety of physiological and pathophysiological states specified within the software. Students can thus collect and analyse expired air generated under different conditions – for example at rest, during exercise and at simulated high altitude.

Recordings can be displayed of ECG and of invasive blood pressure at various sites within the cardiovascular system. Virtual catheters can be located in the systemic circulation within a central vein, the left ventricle or a peripheral artery; within the pulmonary circulation, pressure recordings can be obtained from the right atrium, the right ventricle or the pulmonary artery. The manikin also has the capacity to produce 'urine' from a catheterised bladder, the volume of which can be adjusted according to body fluid status.

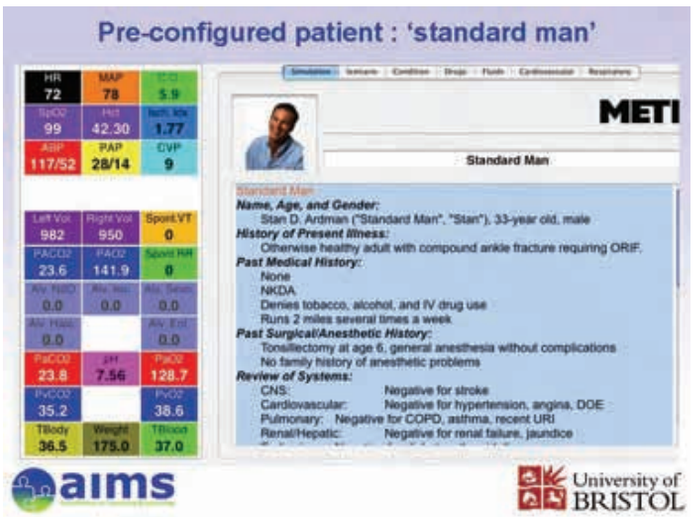
The system includes a range of patients pre-configured within the software but it is possible to configure additional customised subjects to illustrate particular features. Stan's name comes from the baseline preconfigured patient – a healthy young man (Stan D Ardman – get it?) with a broken ankle. The patients and scenarios chosen for each teaching session are selected via drop-down boxes by a technician operating a dedicated G5 Mac computer in a separate Control Room. The technician can also provide Stan's voice via a speaker in the manikin's head.

Human Patient Simulators have traditionally been used for teaching senior medical students and health professionals in a clinical context, particularly in the field of emergency



Above: Judy Harris, Annabel Simms and Giovanni Mann introduce Stan D Ardman to the press at The Society's Bristol Meeting.

Left: Typical waveform display showing cardiorespiratory data.



medicine, and many of the preconfigured patients illustrate clinical scenarios such as shock, haemorrhage and disease. These scenarios can be used to very good effect in illustrating physiological principles and pathophysiology. For example, cardiac function (Starling) curves for a normal and a failing heart can be derived and compared; the power of the baroreceptor reflex (the gain of which can be varied) may be illustrated; and the effects of lung compliance, inspired air composition or pneumothorax on respiratory function in health and disease can be investigated.

The simulator therefore provides realistic, interactive and thought-provoking ways to extend the physiology data that students gather from each other in existing practical classes, and to generate on-line results in situations that are impossible to replicate when data-gathering is restricted to young, healthy subjects who are likely to resist invasive procedures such as the insertion of a left ventricular catheter or the imposition of a pneumothorax! The clinical relevance is particularly valuable for medical and dental students but early feedback suggests that all student groups will find the simulators to be exciting and valuable learning tools.

An additional feature of the simulator is the ability to administer simulated drugs via syringes labelled with bar codes that enable drug recognition software to identify the drug and its concentration. The appropriate physiological/pharmacological response is then initiated via the software. This is useful from a physiological as well as a pharmacological perspective. For example, it is possible to derive a family of Starling curves obtained when different concentrations of an inotrope such as adrenaline are administered.

The simulation suites have been designed with audiovisual links to our teaching laboratories, each holding over 100 students. This will enable us to use the simulators for both small group teaching in place of some tutorials and also in less labour-intensive ways for large group teaching. The visual link to the teaching lab can be switched between displays of the waveform traces and CCTV images of the manikin. Two members of staff can thus provide a live teaching session for over 100 students and we hope in time to be able to transmit the data and images to lecture theatres holding 300 students.

One exciting spin-off from this initiative is a proposal by Giovanni Mann that we collaborate with The Society to broadcast footage of the simulators to schools, in order to foster interest in physiology amongst students at GCSE level and above. The Department already hosts summer schools for organisations such as the Sutton Trust and the National Academy for Gifted and Talented Youth, and we also plan to incorporate the simulators into such events.

Judy R Harris
Department of Physiology, University of Bristol, UK

Bristol revisited

Austin Elliott reflects on the July Meeting

As a student in Bristol more years ago than I care to remember, I don't seem to remember the University being built on a hill! Or rather, I don't remember getting out of breath dashing up the steps from the main building to the Chemistry Department and the Medical School when I was 20. Although Bristol University has a reasonably compact site, the vertical difference between some of the venues came as a slight shock to my middle-aged body. However, it will have ensured less fit delegates (among whom I must number myself) of at least some cardiovascular workout in between biscuits and cups of coffee.

One difficulty of running a large FEPS-style meeting (and Bristol attracted nearly 1,100 delegates) at a university is the problem of trying to get the lecture theatres, the poster venue, the registration desks, and some catering all within easy reach of one another. Demonstrations add another level of complexity. Of course, this is why large international meetings often take place in purpose-built conference centres. The Bristol meeting had most of the lecture theatres on one site (although access to the Medical School through the building works was a minor challenge), with the poster venue 5 minutes away in the University Great Hall, and one lecture theatre in the architecturally imposing Victoria Rooms a couple of minutes further on. This did have the effect of making it difficult to split one's morning between two geographically-separated sessions.

Before the Prize Lecture: Science Minister Lord Sainsbury (left), Alan North, Graham Dockray, Bridget Lumb and (back to camera) Liz Bell.

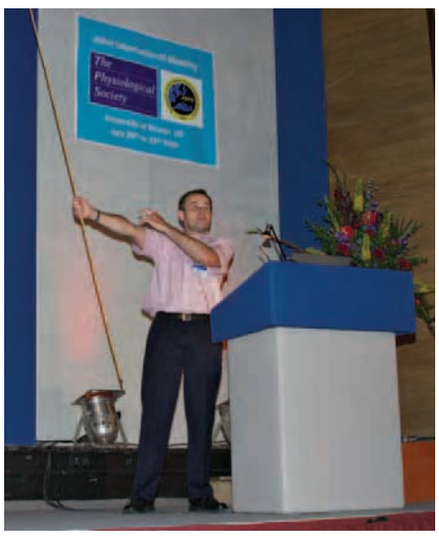
Of course, such slight inconveniences are probably unavoidable given the constraints of running a meeting this size on a university site. My impression was that having the posters separate from the lecture theatre was less irritating than having the lecture theatres 'split up', though in compensation the Victoria Rooms served the Meeting well as a venue for major lectures, including Julian Paton's first Physiological Society Public Lecture. On balance, the geographical 'spread' of the venues did not really detract from proceedings.

The choice of poster venue for a big meeting is always a tricky one. Poster venues can be fancy (large exhibition halls with trade stands and free coffee) or more homely (cramped practical classrooms). As the number of poster presentations at Phys Soc Meetings has expanded, the poster venue problem has become more acute. The choice of the University Great Hall as the poster location for the Bristol meeting worked well, firstly since it meant the trade stands could be in the same place as the posters, and secondly because the grandness of the architecture lent the whole thing a sense of space – although it still got a bit cramped down the aisles of posters when the session was in full swing.

The catering also rose to the occasion, with the lunchtime sandwich bar on the Chemistry Department 'terrace' proving a particular hit. Admittedly, the occasional Sou'wester blowing in off the Bristol Channel did threaten to blow the paper plates (and even sandwiches) off the tables, but in compensation there was a fine view over Bristol.

The welcome reception at the @Bristol Science Centre was a little stingy with the free drinks, but there was compensation in the interesting location, excellent snacks and mercifully short speeches of welcome. Finally, Isambard Kingdom Brunel's engine shed proved an excellent choice of venue for the main dinner. The scale of the building came as a surprise to me – it could easily have fitted a couple of hundred more diners – and shows the strides the City of Bristol has made in imaginatively re-cycling its industrial heritage. The dinner also featured a speech from Science Minister Lord Sainsbury (which can be read on The Society's website), who had previously toured the poster session in the afternoon and also attended Graham Dockray's Annual Review Prize Lecture.

I wanted to close with a word about the Public Lecture, an innovation that ought to become a fixture of Physiological Society meetings. One should not underestimate the work that goes into something like this, almost certainly more than is required for a plenary lecture about (mostly) one's own science. Being asked to do the first ever Physiological Society Public Lecture clearly qualifies as a poisoned chalice – an honour you can't refuse,



Above: Bristol's Julian Paton qualified for the 'poisoned' chalice' and presented the first ever Physiological Society Public Lecture – an innovation that ought to become a fixture at Society Meetings.

Below: Delegates enjoy the sunshine on the Chemistry Department 'terrace'.

Bottom left: Delegates exiting the Victoria Rooms.

but also completely different from a typical scientific talk, probably only usable once and potentially plenty of egg on the face if you are less than sparkling. How Bristol's Julian Paton drew the short straw I don't know, but he rose to the challenge, and even broke the rule about never having live demonstrations of anything (because they are bound not to work). His demonstrations did work, at least mostly, and overall he did an excellent job of showing how modern science helps to address serious real-world problems like hypertension. It is to be hoped that the video of his lecture will find plenty of use promoting physiology in schools and in the community, and that those who follow in his footsteps in giving future Society public lectures will live up to the standard he set.

Austin C Elliott

(*photos by Austin Elliott*) More images of Bristol appear on the inside back cover).

My top 10 papers on biological salt, water and sugar transport

Richard Naftalin (right) makes his 'desert island' selection

Me (R) Guess what?

Wife (B) What?

R *Physiology News* has asked me to write an article on my 10 top papers.

B That's nice – but I didn't think you had written 10 top papers.

R No. No! My 10 favourite papers – The Physiological Society's equivalent of *Desert island discs*.

B You never listen to programmes aimed at us middlebrows. Only that programme for other sad old fogies – *Private passions*.

R Correct, as ever, dearest, but let's pretend – you can be Michael Berkeley and I'll be me, pretending not to sound too pretentious.

B So, Richard Naftalin, your main interest – or more accurately, as I know you quite well – sole interest – is in biological salt, water and sugar transport?

R I wouldn't go that far – but we don't have time to discuss any of that now. Yes, these are the topics that attracted me to physiology in the late 1960s. And one of the people who influenced me strongly then was Aharon Katchalsky. We met when he visited Mill Hill for a few weeks in 1966. He was amazing – charismatic, phenomenally clever, self-deprecating and had had a military intelligence role in Israel's War of Independence in 1948. His papers on irreversible thermodynamics dealing with coupled flows in biological membranes, such as occur with cotransport between glucose, sodium and water in intestine, impressed me a lot then and still do.

B Didn't he die in that dreadful terrorist attack at Ben Gurion airport in 1972?

R Yes, it was horrible. Anyway, my first paper is **Katchalsky A (1967). Membrane thermodynamics in the neurosciences: a study program. Quarton G C, Meinechuk T & Schmitt F O, eds. pp 326-343.** This is a bit of a cheat as it is a review covering Katchalsky's entire work with Ora Kedem. The relationships between hydraulic conductivity, L_p, solute permeability, ω and the osmotic solute reflection coefficient, σ are very clearly explained, along with important ideas about ionic flows through series and parallel membrane arrays of charged membranes.

In the early 1960s, the idea of coupled flows in membranes was quite new, although, interestingly, Starling was aware of the concept 60 years earlier, when he described the balance of colloid osmotic pressure and hydrostatic pressure in capillaries.

In the late 1970s Nick Simmons, Geoff Holman and I used Katchalsky's ideas about negative reflection coefficients to explain intestinal fluid secretion. Irreversible thermodynamics is unfashionable at the moment, mainly because models of coupled flows are viewed in terms of transitions between ligand complexes bound to a carrier protein. Cotransport is assumed to occur by conformational changes in the protein. In contrast, irreversible thermodynamics considers coupling between flows to be generated by frictional interactions between mobile and static elements within the membrane. Conventional cotransport models assume that uncoupled solute leaks via the transporter are due to imperfections in the system, that can simply be factored out of so-called estimates of stoichiometry.

B Mmm, very interesting, but we must get on. What is your second choice?

R This is equivalent to choosing the Choral or Jupiter symphonies, nearly everyone's choice if you would let them. In fact it is, **Ussing H H & Zerahn K (1951). Active transport of sodium as the source of electric current in the short-circuited isolated frog skin.** ***Acta Physiol Scand*** **42, 298-308**. Ussing's paper is a beacon of understanding. It explains how ions are transported across epithelia. In it Ussing introduced the concepts of unidirectional flux, exchange-diffusion, the flux-ratio equation, and solvent drag. He also initiated and defined the terms 'short-circuit current', 'active transport pathway' and 'shunt pathway' and demonstrated active transport of sodium ions in frog skin by combining studies of isotope fluxes with electrical fluxes. Ussing's early papers influenced and shaped all subsequent epithelial physiology and will continue to do so until it is no longer practiced.

B Did you ever meet Ussing?

R Yes – at Mount Desert Island Biological Laboratory, where we spent several summers working with Arnost Kleinzeller. He and Arnost were old friends.

B So what else do you have?

Figure 1. Curran's first three compartment model for Na coupled water transport

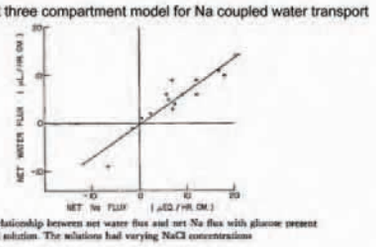


FIGURE 1. Relationship between net water flux and net Na flux with glucose present in the mucosal solution. The solutions had varying NaCl concentrations

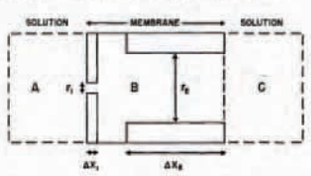


FIGURE 3. Schematic model system for water transport. *A* and *C* represent external solution, *r* and Δx represent pore radius and membrane thickness respectively.

R Well, the next choice is **Curran P F (1960). Na^+, Cl^- and water transport in rat ileum *in vitro*. *J Gen Physiol* 43, 1137-1148**. Peter Curran brought Ussing's concepts and techniques to the intestine. He showed how transepithelial water movement is osmotically coupled to active salt movement. Before this paper there had been much confusion about the mechanism of water movement across epithelia. It was considered that water flow was powered by a vital force. Curran showed definitively that water movement was dependent on active sodium ion movement across the intestine and suggested that NaCl accumulated in a central compartment, thereby generating osmotic pressure across the tight apical barrier which leads to coupling of water flow from lumen to blood with net Na^+ movment. (Fig. 1). Oddly, this standing-gradient theory is generally credited to Jared Diamond who published a similar model 2 years later. In this paper he equated Curran's central compartment with the physical entity of the lateral intercellular spaces which are bounded by membranes containing Na^+ pumps.

B You knew Peter Curran?

R Yes I worked in his lab for a few months in 1972. He introduced me to the methods of intestinal transport physiology and we also did some quite interesting work together.

B He died very young?

R Yes, his death in 1974, shortly after we published our paper on bidirectional galactose fluxes in rabbit intestine, was a catastrophic loss to epithelial physiology.

B Why do you say that?

R For the 20 to 30 years after Peter's death intestinal physiology became very dogmatic; he might have prevented some of this as he was very influential.

B What is your next choice?

R Next is another landmark paper in epithelial physiology, **Schultz S G & Zalusky R (1964). Ion transport in isolated rabbit ileum. II The interaction between active sodium and active sugar transport. *J Gen Physiol* 47, 1043-1059**. Both Curran's and Schultz's work were derived directly from Ussing. Stanley Schultz showed using short-circuit current measurements and ion flow measurement (Fig. 2), that Na^+ movement across rabbit ileum is coupled to glucose movement and vice-versa. This quantified Robert Crane's observation that there is Na^+ gradient-dependent accumulation of glucose across intestinal brush border membranes.

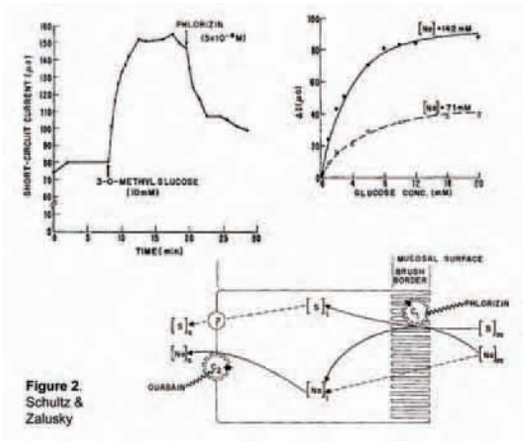


Figure 2. Schultz & Zalusky

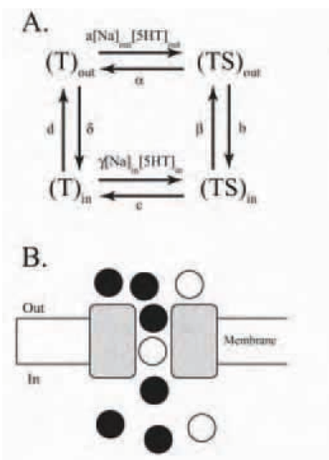


Figure 3. Adams & deFelice

A) Represents the alternating carrier model of Na^+ -serotonin cotransport

B) The long pore model with three solute binding sites in series black represents Na and white serotonin.

By the mid 1960s, the essential features of Na^+, sugar and water interactions in epithelia had been described. Although later technology employing brush border membrane vesicles and expression cloning of purified sodium-glucose transporter SGLT's in oocytes are marvellous technical achievements, their main role is to ratify and precisely locate the transport phenomena that had been previously elucidated by the papers already mentioned. We still do not really understand how sugar and water and Na^+ are coupled within the transporter and the role of leaks in this process.

B You have met Stanley Schultz?

R Oh yes, he is a wonderful lecturer and was a good friend of Peter Curran and Arnost Kleinzeller and one of the leading scientists at Mount Desert Island Biological laboratory at the time we visited.

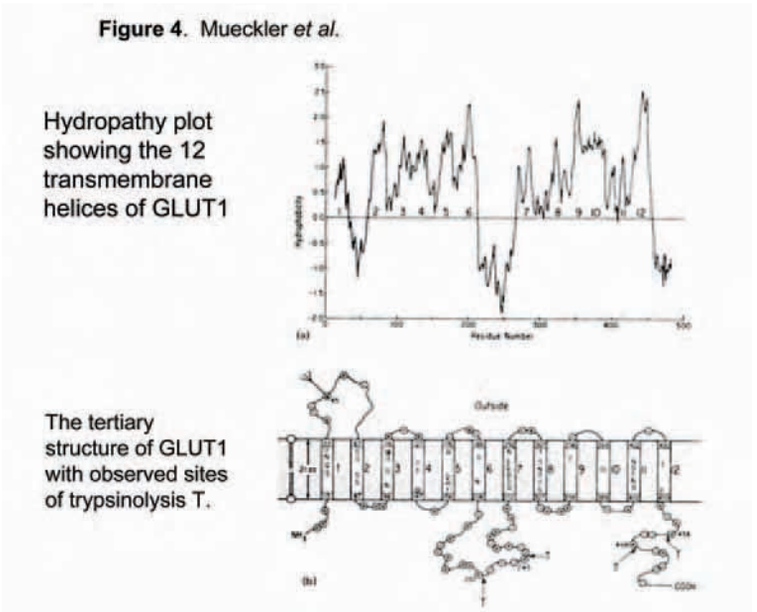
B So what is your next choice?

R Well I am going to jump forward nearly 40 years to **Adams S V & deFelice L J (2003). Ionic currents in the human serotonin transporter reveal inconsistencies in the alternating access hypothesis. *Biophys J* 85, 1548-1589.**

B A 40 year jump; that seems a little odd?

R Well that's the time it has taken for the field to unburden itself from the yoke of dogma laid down by the 'titans of the 60s', in particular with the heuristic of alternating carrier models.

In a remarkable series of papers on serotonin transporter kinetics, deFelice and his colleagues have demonstrated that serotonin transporter, cloned into *xenopus* oocytes behaves in many ways



Reproduced from *Science* 1985 **229**, 941-945

like a long pore, similar to that described by A L Hodgkin & R D Keynes in 1955 (*J Physiol* **128**, 61-88) for K^+ transport in squid axon. Solutes are driven through a narrow pore by others pushing from behind (Fig. 3B). Importantly, they have demonstrated that both sides of the serotonin transporter are exposed simultaneously to ligands. With the alternating model only one side at a time can be exposed to ligand (Fig. 3A).

B Why is this so important?

R Well, it means that the heuristic explanation, as in Fig. 3A, no longer satisfactorily explains at least one instance of cotransport. DeFelice has recently shown new discrepancies between binding and transport of noradrenaline – but we do not have time to go into this.

B Can you explain in jargon-free terms what you mean by heuristic thinking.

R Yes, heuristic thinking is expression of an abstract idea like cotransport in terms of a picture diagram, for examples see Fig. 3A or 3B which you assume, for want of better, to be the solution to the problem. The snag is that once the diagram is drawn and is seen to give a plausible explanation, it often becomes concretized as a 'thought object' and if enough people believe in it – then that is how things are; *'Es muss sein, Ja'*. Katchalsky often use to say, only half-jokingly, that the most important commandment of thermodynamics is *Thou shalt not make a graven image*. DeFelice's findings now supply a plausible physical basis, i.e. a frictional model for cotransport, which has been spectacularly absent from previous cotransport models. This makes me very happy!

B Okay, so you like seeing cherished ideas toppled?

R Yes, iconoclasm is in my blood. Our ancestor, Abraham, from South Iraq was very keen on it too – for a day or so.

B Enough already! So what's your next choice?

R Something completely different. **Schnermann J, Chou C-L, Ma T, Traynor T, Knepper M A & Verkman A S (1998). Defective proximal tubular fluid reabsorption in transgenic aquaporin-1 null mice. *PNAS* 95, 9660-9664.** Using mice genetically modified to be deficient in aquaporin 1, the authors show by microperfusion and micropuncture that the deficient renal proximal tubule has only 20% of the water permeability of wild type mice. The knockout mice were unable to concentrate urine to more than 500mOsm, unlike wild type mice that concentrated urine to 1080mOsm. This paper demonstrates that paracellular water flow across the proximal tubule is unlikely – if it existed, then there would not be such a large difference between the osmotic permeability of knockout and wildtype proximal tubules. It is an easily understandable illustration and a marvellous demonstration of the power of this genetic technique to elucidate physiology.

B So what is your next choice?

R For the rest of the programme I will select papers dealing with passive facilitated glucose transport. **Sen A K & Widdas W F (1962). Variations of the parameters of glucose transfer across the human erythrocyte membrane in the presence of inhibitors of transfer. J *Physiol* 160, 404-416.** This and its accompanying paper are among the key papers in all transport physiology. These papers showed how to quantify glucose transport in similar ways to enzyme kinetics. Using a simple method of monitoring glucose movement by following the light scattering changes in human erythrocyte caused by cell volume changes occurring during net glucose efflux, they showed that there are internal and external aspects to glucose binding to the transporter. Widdas has had a huge influence on transport physiology, in methodology, theory and in discovery of the mechanism of several inhibitors. He did it all with homemade equipment and with only a very few loyal coworkers. Chief amongst them was Graham Baker.

B You thought a lot of Graham didn't you?

R Yes, it was a real privilege to have worked with him. He was very effective and a sobering influence. We wrote a paper together in 1979 on the apparent differences in glucose affinity on the inside of the transporter dependent.

B And your next choice?

R Mueckler M, Caruso C, Baldwin S A, Panico M, Blench I, Morris H R, Allard, W J, Lienhard G E & Lodish H F (1985). Sequence and structure of a human glucose transporter. *Science* 229, 941-945. This paper is another of the key papers in transport. It unravelled the primary, secondary and tertiary protein structure of a glucose transporter. It has had an enormous influence and was precursor of many hundreds of papers on transporter structure in the whole of biology. The positions of the 12

transmembrane helices obtained by hydrophobicity plots are shown (Fig. 4). These have stood the test of time amazingly well. Sequence mapping of the glucose transporter links transport with genetics and protein chemistry and concentrates our attention on the nature of the physico-chemical interactions between the sugar ligand and transporter. But, unfortunately, it does not show us where the glucose binding site(s) are.

B And you next choice is?

R Cloherty E K, Heard K S & Carruthers A (1996). Human erythrocyte sugar transport is incompatible with available carrier models. *Biochemistry* 35, 10411-10421.

B I think I see your Abrahamic tendency re-emerging.

R Yes, facilitated glucose transport has also been dominated by the alternating carrier heuristic since the 1950s. It is one of the most pervasive models in modern biology and very few people have had the courage to challenge it. But Tony Carruthers has.

B I remember him as one of Peter Baker's turbocharged PhD students. Is he still as energetic?

R Yes, Tony's scientific struggle would make Sysiphus wish he had stayed with the stone rolling. However, persistence (Tony's) and great experiments have paid handsome dividends. The veneer shielding the alternating carrier model from critical appraisal is cracking.

B So what does this paper show?

R The effects on external or internal D-glucose on cytochalasin B binding to GLUT1 in human erythrocyte membranes are examined. Since the inside facing site of GLUT1 has a lower affinity for sugar than the outside site, one would predict that a high inside sugar concentration should not cause a large displacement of cytochalasin B binding, but in fact it does. This means that the predicted glucose affinity asymmetry obtained from sugar fluxes differs from that obtained with competitive ligand binding at equilibrium. These data are consistent either with an alternating carrier or a fixed two-site transporter with symmetrical affinities. These findings confirm that the observed transport asymmetry is produced by a resistance to sugar flow at the cytoplasmic surface of the transporter that retards sugar equilibration between the membrane surface and the remainder of the cytosol.

B So the carrier model is wrong?

R Well from this paper it appears very shaky and several other papers from Carruthers' lab and my lab have made it even less plausible. But kinetic and thermodynamic results are ambivalent and it is unsafe to discount a mechanism on the basis of one kind of experiment. What is needed now is molecular docking and molecular dynamic studies showing the precise location of the glucose binding pathway and the kinds of interactions with the amino acid side chains and water that occur with transported sugar.

B That sounds like a manifesto.

R It is really and I think we are near the threshold of achieving these goals.

B That must be very exciting for you all.

R Absolutely, and it will be very useful too.

B So what is your last choice?

R Salas-Burgos A, Iserovich P, Zuniga F, Vera J C & Fischbarg J (2004). Predicting the three-dimensional structure of the human facilitative glucose transporter GLUT1 by a novel evolutionary homology strategy: insights on the molecular mechanism of substrate migration, and binding sites for glucose and inhibitory molecules. *Biophys J* 87, 2990-2999. Since the 3-D structure of transporters in the major facilitator superfamily (MSF) is common to all family members, it is possible to thread the amino acid sequence of protein like GLUT1 with an unsolved 3-D structure onto the 3-D template of a protein like Lac permease which has been crystallized and solved by X-ray crystallography very recently (Abramson *et al.* (2003). Structure and mechanism of the lactose permease of *Escherichia coli*. *Science* 30, 610-615). The Salas-Burgos paper shows that the 12 transmembrane helices surround a central water filled pore which is divided into an outer conoid opening, a narrow central pore and a wide internal vestibule surrounded by the interhelical chains projecting from the endofacial surface of the transporter (Fig. 5). The relatively long length of the pore which can accommodate at least six glucose diameters and the complexity of its pore shape and the wide separation between external phloretin and internal cytochalasin B binding sites indicates that there are more than a single glucose binding site.

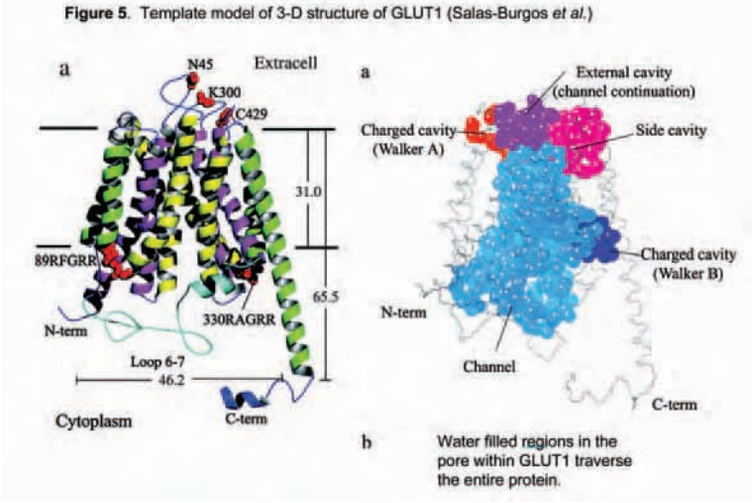
B So this paper is the reason why you seem so confident that a clear solution to the glucose transport problem will be found soon?

R Yes.

B Well, thank you, Richard Naftalin.

R Thank you – it has been a pleasure.

Figure 5. Template model of 3-D structure of GLUT1 (Salas-Burgos *et al.*)



A short month in the life of the Vice Chair

Ian McGrath reflects on a busy February

February is the low point of my year. Glasgow is still too dark and cold. Mardi Gras beckons, but not here. Keep busy then.

Start with reconnaissance mission to The Society's Publications Office in Cambridge. Chairman (me next year) is responsible for this operation as well as the London Office, though, in practice, the Chairman of *The Journal of Physiology* and the Managing Editor, Carol Huxley, make it tick, quietly and efficiently. I am enormously impressed with this operation, which produces *The Journal of Physiology*, *Experimental Physiology* and *Physiology News*. The staff is settled, experienced, effective and gives a level of enhancement to the publications largely invisible to readers and authors but which explains their success, and hence bankrolls The Society.

Home to GU to address second year medics. The 'new' (10 years old) course has no 'lectures' so I stand in a room of 250 seated students and deliver a 'Plenary', called *Control of blood vessels* in the Cardiovascular Block. I have another Plenary in an earlier Neuroscience Block on *Pharmacology as exemplified by the ANS*, or some such nonsense, so am proud to have subverted the system by putting on a two non-lecture series.

The Falkirk wheel where boats are lifted 100 feet

In the afternoon I chair a meeting of our Exercise Science Group which is, as you might expect, brimming with energy and enthusiasm. They got a 5* in the last RAE which provides some chutzpah for dealing with the inevitable biochemists who run our faculty.

Off to Birmingham for a research seminar. Go on too long, as usual, but they are very polite about it. Interested to see how physiology is faring. Views are mixed on this and staff is spread about a bit, but good science is surviving, so I am optimistic.

Next comes a lecture to dental students. I get to do all the lectures starting with 'anti-'. Today it is anticoagulants, which I optimistically hope will raise more interest than antidepressants and antipsychotics did last term. On to my honours project students, where I indulge my prejudices by making them find out about *The myth of the adrenaline surge* and *The difference between a drug and a food supplement*. It always amazes me how each one finds an individual approach and acquires their own unique prejudices.

Mid-month, off to Seville to organise a symposium at the joint meeting (reported in *Physiology News* **59**, 7). Sun at last. Visit one of my favourite places, Cadiz, where the 'Carnival' is taking place. Crazy people, communal singing in the streets, on bin-lorry/floats, wherever. Great.

On return, immediately back to The Society's Administration Office in London for job interviews. From a very good field we appoint Donna Brown to the Education Officer post. (She has made a flying start and we look forward to great success in this area).

At weekend, nearly freeze to death in NE wind attempting a recreational cycle along canal from Glasgow to Edinburgh. Might have hoped for prevailing SW tailwind. Cross entire country at virtually same height except

Ian McGrath faces a north east wind cycling along the canal from Glasgow to Edinburgh (above) and reverts to Vice Chair mode (below).

at fantastic Falkirk wheel where boats (but unfortunately not bikes) are lifted up 100 feet. Travelogue – visit this: well worth it.

Back home to chair a PhD Viva, lecture on 'anti'-hypertensives, then take my seminar group of penultimate year physiology students. Their course is pretty generic so the seminars are an attempt to put in some physiology. We are currently building on this with a new course that clarifies what is generic (to pharmacology, neuroscience, physiology, anatomy) and wraps subject-specific stuff around this. Fingers crossed.

PhySoc Executive Committee beckons so back on Easyjet to Stansted. On time, nice train to Liverpool street. Return via hell-hole of Heathrow and delayed BA flight, as usual.

This week ends with a Divisional Staff Meeting. Asked to consider divisional restructuring, staff decide that they like

things the way they are. I am quietly pleased since I still have the bruises from the previous restructuring when I persuaded them to create this current status quo. However, the déjà vu has an ominous ring.

Week starts with the PhySoc Council Meeting. Dinner night before allows everyone to network and be safely in town for 9 a.m. start. Excellent round-table discussion on science politics with very erudite guests, including our former President and current MRC Chief Colin Blakemore, Ian Gibson MP and BSF President Tom Blundell. Gibson announces date of election and predicts result.

Back to the farm for research meeting with my colleague Craig Daly, who has put up with me for over 20 years, and visiting professor Elisabet Vila from Barcelona. She is on sabbatical and, perversely, is spending February in Glasgow, presumably on some sort of exchange with the substantial fraction of our population who wisely think Spain is a safer bet. We plot to outwit idiotic referees who so comprehensively misunderstood our latest joint manuscript (note added September – it's out online in *Br J Pharmacol*).

Monday 28th, RAE panel has first meeting in Manchester. It's been a long shortest month. Spring-time tomorrow.

Ian McGrath
Vice Chairman, The Physiological Society Executive Committee

How were you turned on to physiology?

Send us your own personal stories, with 'then' and 'now' photographs if possible, for publication in future issues of *Physiology News*.

The next copy deadline is Friday, 6 January and contributions should be sent to lrimmer@physoc.org

What turned you on to physiology?

For Thelma Lovick it was two Poles, a Russian and an Englishman ...

There was no great defining moment. It was more a sort of progression of events. I wasn't doing biology at A-level but I quite enjoyed chemistry and was vaguely wondering about doing a degree in biochemistry. Then I came across T H Huxley's book *Elementary lessons in physiology* in a local charity shop. It was only 2/- so I bought it and I quite liked it. I thought I'd do physiology. Manchester interviewed me and must have thought I was worth the risk because they gave me a place.

I wasn't the most diligent of students and at the beginning of the final year I hadn't really thought about the future. Then one day I was in a practical run by Henry Bobinski where we were making red cell ghosts to study sodium transport. He remarked that I might make a good research worker. I was a bit surprised as I hadn't thought I was in that league at all! I'd done a summer job in the bacteriology lab of a local dairy, mainly washing out and sterilising an unending stream of glass roll tubes and petri dishes (no disposable plastics in these days). Occasionally they let me out from the tropical heat of the autoclave room and into the labs where I must have become sufficiently adept at handling test tubes for Henry to notice!

After a few days I went to see Henry and asked what you had to do to get into research. He advised me to write round to different departments. So I did and several departments invited me to visit. I thought I would like to work on muscle and King's and Bristol seemed interested.

But I had to get a degree first. In those days at Manchester you had to do two short research projects in the final year. I did a renal project first and then I chose to do a neurophysiology one with Derek Paul, recording from cerebellar Purkinje cells in decerebrate cats. That was good. At about that time I'd also

Thelma Lovick, pictured (top) as a student and (below) today, wasn't the most diligent of students but encouragement from Henry Bobinski to take up research led her to Birmingham University where she has stayed throughout her career.

come across a little book in the library by I M Sechenov entitled *Reflexes of the brain*. I read it during the vacation. It was almost as much philosophy as neuroscience and something just clicked. As soon as I got back to Manchester I bought my own copy, which I still have.

I didn't do very well in my finals, so thoughts of King's or Bristol receded.

Then during the summer Birmingham got in touch and asked me to come for an interview. I wasn't that keen on the idea of Birmingham as a place to live but I went anyway and by the end of the day I was being offered a studentship for a muscle project. But I didn't want to do that any more! During the afternoon I'd visited Andrzej Zbrozyna's lab and now I wanted to work on the neurophysiology of conditioning and learning. I announced this to the interview panel (can you believe the arrogance of youth?). There was a sort of stunned silence and I was asked to wait outside. And then to go home. I'd blown it.

But I hadn't … a week or so later there was a phone call from Birmingham! I'm still there now, although I abandoned conditioned reflexes a long time ago. So there you have it – what turned me on to physiology? Two Poles, a Russian and an Englishman – simple as that.

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

... for Bill Winlow it was J Z Young

Like a number of other physiologists I know, I started academic life as a zoologist, but with two years of physiology as a subsidiary subject. During that time at the University of Newcastle upon Tyne, physiology was both better organised and better taught than zoology with the likes of AA Harper, Eric Blair and Alan McComas on the staff, and I rapidly began to realise that I was interested in how animals worked. At that point a new head of zoology arrived from Bristol, RB Clark (author of *Dynamics in Matazoan Evolution)*, who started reorganising the Zoology Department. In the summer before my final year I chose one of his vacation projects on the evolution of nervous systems, during which time I discovered J Z Young's book *A Model of the Brain*, which was about how we might begin to 'understand' the octopus brain. Suddenly form was related to function and I knew that I wanted to work on nervous systems.

For my PhD, I went to the Gatty Marine Laboratory at St Andrew's University to work on motor control in lobsters with Mike Laverack, combining morphological studies with electrophysiology. I then did three postdoctoral fellowships, the first in Glasgow Zoology Department with Peter Usherwood, where I learned electron microscopy and combined it with electrophysiology to study degeneration at mouse motor nerve terminals. Later, I went to work with Eric Kandel in New York and spent a substantial amount of time working out the structure of *Aplysia* neurons using cobalt chloride injections – I still have pictures of my drawings hanging on my study wall at home.

After New York I went to the University of Sussex and spent a very happy period working on another mollusc, *Lymnaea stagnalis*, with Paul Benjamin. During my last year in Sussex I was a temporary lecturer in animal physiology. That opened the door to an appointment as Lecturer in Physiology at Leeds, where I was appointed on the same day as David Cotterell.

For my first presentation to a Physiological Society Meeting, I used too many slides to explain the morphology of *Aplysia* neurons and was defended by none other than J Z Young! The paper was accepted and I felt that the wheel had come full circle. Thank you J Z for a career in physiology – it still goes on, because although I now spend a lot of my time writing about anaesthesia and reporting on anesthesiology conferences, most of what I write about is applied physiology.

Bill Winlow
Emeritus Professor of Neuroscience and Medical Writer

... and for Austin Elliott it was a physicist

I am not sure that 'turned on to physiology' quite fits for me. l became a physiologist of sorts – not sure I've ever been a 'proper' anything – quite by accident, having started out doing a BSc in chemistry with subsidiary biochemistry. Indeed, when I became a PhD student in a physiology department (at UCL) I had only the vaguest idea of what physiology was. (The departmental postgraduate tutor must have noticed this, as he insisted I sit through the first year undergraduate physiology course – I was annoyed about this at the time, but he was probably right). If I am a physiologist now I became one not just by doing research in physiology, but also by having to teach physiology, particularly to medical students. The problem-based learning medical courses get a mixed press (including in these pages) but they are very good for introducing physiology lecturers to some real-world integrative physiology.

One incident that stands out in retrospect is a seminar l went to in my final year as an undergraduate. Biochemistry courses in those days typically involved an incomprehensible introduction to enzyme kinetics (the incomprehensibility seemed to be a source of pride for the lecturers) and then a laborious trudge through all (and I do mean all) the enzymes of the glycolytic pathway. Despite this powerful aversion therapy, l ended up doing my final year research project on enzyme kinetics. One day I saw an announcement for a seminar in the Biochemistry Department by David Gadian,[1] one of the pioneers of applying NMR spectroscopy to intact tissues in the late 1970s and early 80s, about 'doing enzymology inside live cells with phosphorus NMR' or something similar. Sitting through this seminar I was fascinated by the way that NMR seemed to be re-writing the book on enzymology. Time after time Gadian's seminar showed that the regulation of glycolysis worked out in the test-tube, typically with small amounts of enzyme and infinite amounts of substrates and cofactors, was a poor predictor of what happened in real cells. The glycolytic enzyme biochemists in the audience seemed non-plussed, and it was clear that directly measuring parameters inside living cells was the only way to go. More than 20 years later I still think so. The seminar was instrumental in my going on to doing a PhD at UCL with Joan Dawson,[2] and latterly with David Allen,[3] using phosphorus NMR to measure metabolism in living muscle, although after my PhD I soon moved on to using fluorescent dyes and microscopy to make measurements of intracellular [Ca^{2+}], pH, metabolism, and other things. Had I known then that this would condemn me to two decades of repeatedly cleaning crystallized salt and sticky green sludge out of the insides of inverted microscopes I might have taken a different career path! But that, as they say, is another story.

[1] Then working in the Oxford Biochemistry department with George Radda, now at the Institute of Child HeaIth and a joint winner of the 2003 Ig Nobel Prize for his imaging work showing London Taxi drivers have surprisingly large brains: see: http://www.improbable.com/ig/ig-pastwinners.html

[2] Currently Associate Professor of Physiology at the University of Illinois Urbana-Champaign, Joan is the wife of magnetic resonance imaging (MRI) pioneer Paul Lauterbur, see *Physiology News* **55**, 12.

[3] Now Professor of Physiology at the University of Sydney, and an occasional *Physiology News* contributor.

Letter from ... Russia

Evgeny Nikolsky and Ellya Bukharaeva report from Kazan Scientific Centre of the Russian Academy of Sciences, recently awarded a Society Centre of Excellence grant, on investigations of the neuromuscular junction

Kazan is a city situated on the bank of the Volga River and will celebrate its 1,000th anniversary in 2005. The city is now one of the biggest scientific centres in Russia. Its university was founded in 1804 and, since then, many important discoveries have been made there in the field of natural sciences. These include discovery of the chemical element ruthenium, the phenomenon of electron paramagnetic resonance, and the process of oxidative phosphorylation.

The Kazan physiological school is one of the oldest in Russia, and has traditionally had particular strengths in the physiology of the neuromuscular system. The Laboratory of the Biophysics of Synaptic Processes, which was founded on the base of the Kazan State Medical University and the Kazan Institute of Biochemistry and Biophysics of the Russian Academy of Sciences, is currently one of the centres of cellular neurophysiology in Kazan. The head of the Laboratory is Evgeny Nikolsky. In addition the group includes one senior research associate, six postdocs and three PhD students. Our laboratory is currently doing research in several areas of biophysics and the physiology of synaptic processes.

In the 1980s, in close collaboration with colleagues from the Institute of Physiology of the Academy of Science of the Czech Republic (Frantisek Vyskočil and Stanislav Tuček), we

Evgeny Nikolsky (left) and Ellya Bukharaeva

began investigating the mechanisms and physiological significance of non-quantal release of acetylcholine (ACh) from motor nerve terminals. We found that this component of release, which accounts for up to 95% of the ACh in the synaptic cleft at rest, is a process of active transport and is not simply leakage of cytoplasmic ACh. This transport of ACh is associated with the high affinity system of choline uptake into the nerve: its efficiency depends on the amount of choline in the extracellular space and it is blocked by hemicholinium-3. Comparison of spontaneous quantal and non-quantal secretion at different times after nerve crush and regeneration showed that block of non-quantal secretion is one of the first reactions to the trauma. Thus non-quantal secretion stops within 3 hours after nerve crush, while spontaneous quantal secretion persists for at least 15 hours. Conversely, during reinnervation of the muscle, non-quantal secretion recovers at least 3 days before spontaneous quantal secretion (Nikolsky *et al.* 1996). Impairment of non-quantal secretion leads to changes of the resting membrane potential in the synaptic area. Thus the hyperpolarisation of 2-3mV that is normally present in the synaptic zone disappears when non-quantal release is abolished in a variety of ways, including block of Na-K ATPase. This proves the important role of non-quantal release of ACh in the regulation of the membrane potential of the muscle fibre in the synaptic zone and its link to changes in activity of the sodium-potassium pump (Nikolsky *et al*. 1994).

Our other main field of research is the investigation of the regulation of quantal release by activation of presynaptic receptors for ACh and co-transmitters (ATP, glutamate). We have found that ACh appears to act by independent mechanisms to depress both spontaneous release (by activation of presynaptic mAChRs) and evoked release (by activation of nAChRs on the nerve terminal). The depression of evoked release appears to be mainly caused by changes of a calcium-activated potassium current in the nerve terminal. The effect on spontaneous secretion is mediated by pertussis toxin-sensitive and -insensitive mechanisms which are associated with the final stages of exocytosis, downstream of calcium entry into the nerve.

More recently, we have been studying the kinetics of evoked quantal release of ACh from motor nerve terminals of mammals and frogs. We have found that the physiologically active substances norepinephrine and ACh can respectively increase or decrease the degree of synchrony of quantal release (Bukharaeva *et al*. 1999; Nikolsky *et al*. 2004). Synchronization of evoked quantal release by norepinephrine is mediated by activation of presynaptic beta-adrenoceptors and activation of adenylate cyclase and protein kinase A (Bukharaeva *et al*. 2002). Mathematical modelling has shown that the observed

The Russian Academy of Sciences with the Lobatchevsky monument in the foreground

changes of kinetics of release would have a significant impact on the amplitude and time course of synaptic responses, thus contributing to the efficiency of synaptic transmission.

In our group we place great emphasis on the education of young scientists who are doing PhD projects in our laboratory. In this regard we regularly organise Russian Schools for Young Scientists covering current problems of neurophysiology. In May 2005 we hosted an IBRO Workshop in Neuroscience with internationally respected neuroscientists including Jack McMahan, John Nicholls, Andrea Nistri and Clarke Slater. In addition, we make a big effort to develop and maintain fruitful co-operation with international colleagues. Young scientists educated in our laboratory have frequently spent extended periods of time working in leading neurophysiological laboratories all over the world, including those of Miriam Salpeter (Cornell, USA), Yves Ben-Ari and Peter Bregestovsky (INSERM, Marseille, France), Maria Bykhovskaya (Lehigh University, USA) and Clarke Slater (Newcastle University, UK). We make regular visits to the Institute of Physiology of the Academy of Science of the Czech Republic.

In spite of the successful development of our laboratory, there are serious problems with finances. In recent years, we have been fortunate to obtain some funding from both Russian and international sources. For example, in 2004, in collaboration with Clarke Slater, we obtained a Royal Society Joint Research Grant for studies of quantal release from mouse neuromuscular junctions during recovery from botulinum toxin A. A Centre of Excellence grant from the Physiological Society funded components of our Olympus fluorescence microscope which is being used in this work. Together, all the grants we received last year amounted to about $30,000. This included funding from all the available sources in Russia. While this total is an enormous amount in Russia, it left us with a major problem: deciding how much of the money to spend on salaries and how much on laboratory consumables. With such a low level of financial support, the purchase of even core equipment for our laboratory is virtually impossible.

Clockwise from top left: Mathematical Faculty of Kazan State University and the National Library; Kazan Kremlin; on the Volga River

People often ask us how, in times that are so difficult for Russian science when not just individual laboratories but whole Institutes are being closed, we have been able not only to maintain but also to develop the scientific potential of the laboratory. In reply, we can mention three main points: first, we have concentrated our forces and funds on the areas of our established scientific strength without trying to adopt other, perhaps more fashionable, approaches. Second, we have tried to attract bright young people who have a strong, almost romantic, commitment to their research. Third, we have developed and maintained close collaboration with foreign colleagues who have given us substantial support of many kinds.

The successful broadening of our international collaborations in the last decade gives us hope that in the future we will be able to establish an international centre for the education of young neuroscientists in Kazan. In that centre, young scientists from throughout Russia and abroad could study practical aspects of neuroscience and carry out PhD projects using modern methods. The training and experience they would receive would help them in their scientific careers and in developing possibilities for work abroad.

Acknowledgment

We thank Clarke R Slater for his help with the translation of this article.

Evgeny Nikolsky
Ellya Bukharaeva

Department of Biophysics of Kazan State Medical University, Laboratory of Biophysics of the Synaptic Processes of Kazan Institute of Biochemistry and Biophysics of Kazan Scientific Centre, Russian Academy of Sciences, Kazan, Russia

References

Nikolsky E, Zemkova H, Voronin V & Vyskoèil F (1994). The role of non-quantal release in surplus polarization of mouse diaphragm fibres at the endplate zone. J. Physiol 477, 497-502.

Nikolsky E, Oranska T & Vyskoèil F (1996). Non-quantal acetylcholine release in the mouse diaphragm after phrenic nerve crush and during recovery. Exp. Physiol, 81, 341-348

Bukharaeva E, Kim K, Moravec J, Nikolsky E & Vyskoèil F (1999). Noradrenaline synchronizes evoked quantal release at frog neuromuscular junctions. J Physiol 517, 879-888.

Bukharaeva E, Samigullin D, Nikolsky E, & Vyskoèil F (2002). Protein kinase A cascade regulates quantal release dispersion at frog muscle endplate. J Physiol 538, 837-848.

Nikolsky E, Vyskoèil F, Bukharaeva E, Samigullin D & Magazanik L (2004). Cholinergic regulation of the evoked quantal release at frog neuromuscular junction J Physiol 560, 77-88.

The case for microgravity research

Why should UK life scientists be excluded from the opportunity of using space agencies' resources to study problems of major physiological and clinical interest?

Marco Narici (left) and Michael Rennie

A few days ago (19 September), NASA's administrator Dr Michael Griffith announced detailed plans for returning to the Moon by 2020. The intention is to establish a permanently manned lunar station, with crew shift durations of up to 6 months, and eventually, to extend human presence in the solar system and beyond.

However, before these long-term goals can be achieved, there are a number of obstacles that need to be overcome. Exposure to microgravity notoriously affects the major physiological systems, amongst which the musculoskeletal, cardiovascular, nervous, hormonal and immune systems are the most affected. Pertinantly, whereas changes to the cardiovascular, nervous, hormonal and immune system are reversible within a relatively short time upon return to life at 1 g, and some may be mitigated by in-flight exercise countermeasures (e.g. the cardiovascular, the respiratory and motor control changes), those affecting the musculoskeletal system are more difficult to protect and to reverse. It has been estimated that the loss of muscle and bone may be as much as 1-2% per month under weightless conditions, a rate which would render a 36 month trip to Mars and back extremely hazardous for the participants, who would suffer a grave risk of their remaining lives as cripples on Earth. However, muscle atrophy and osteopenia are not only a problem upon return to 1 *g*, but also during spaceflight since preservation of mobility is vital for tasks such as extra vehicular activities (EVAs) and during surface activities, dealing with emergencies. Another major problem is that of shielding astronauts from solar radiation, but although this is likely to be difficult, it should not be insuperable.

Nevertheless, one fundamental issue is that the long-term effects of exposure to spaceflight conditions are actually unknown. For example, the bone loss is apparently reversible after 1-2 years but the changes in bone microstructure do not seem to be fully reversible. Another isssue of great concern is the effect of trace gases and changes in microflora on an already weakened immune system, which may lead to an increased cancer risk in the long term.

The major space agencies (National Aeronautics and Space Administration (NASA), European Space Agency (ESA), Japanese Space Agency (JAXA), Russian Space Agency (Roskosmos) and now even China) invest vast funds each year in support of research programmes aimed at the study and prevention of the physiological deconditioning induced by actual and simulated microgravity. As far as ground-based studies are concerned, Europe can claim some of the best facilities for short and long-term bed rest experiments, the French Institute for Space Medicine and Physiology (MEDES) (www.medes.fr) and the German Aerospace Centre (DLR) (www.dlr.de/me). For 2002-2006 alone, ESA has committed about €90M to human spaceflight and microgravity research: it is just about to launch a new 3 year campaign of short (5 day) and long-term (60 day) bed rest studies. These initiatives are of great scientific interest since they provide the opportunity to perform many investigations on healthy individuals undergoing bed rest under highly controlled conditions and with access to excellent wide range facilities such as magnetic resonance imaging (MRI), dual-energy X-ray absorptiometry (DEXA), micro-computed tomography, human centrifuges, climate chambers, rotating chairs, lower body negative pressure, high resolution echography and tissue engineering, to mention a few.

For instance, in one of the recent bed rest studies organised by ESA at the MEDES clinic in Toulouse (http://www.medes.fr/Clinic/Experiments/LTBR/), we were able to demonstrate that about 30% of calf muscle mass is lost after 90 days of inactivity (Fig. 1), even though individuals performed regular, high-intensity, exercise countermeasures effective in preventing atrophy of the thigh muscles (Reeves *et al*. 2005; Alkner and Tesch, 2004). From a clinical point of view, such loss of muscle mass is particularly concerning since a loss of muscle mass greater than 40% is normally considered a serious health-hazard (Morley *et al.* 2001). As a matter of fact, over four and a half months on the Mir Space Station astronaut 'A' lost 40% of his body's muscle mass, 12% of his bone mass, and 23 pounds. After astronaut 'A' returned to Earth it took six months to recover the lost strength, and a year to recover the lost bone mass. Two other astronauts who stayed over four months still have bone deficits after more than 2 years on Earth (see NASA archives: http://members.nova.org/~sol/station/hazards.htm) Thus, it appears that unless some means is found to create artificial gravity in space, for example by building a vehicle which spins around its axis with living quarters at the periphery or an exercise device which itself produces gravity (di Prampero & Antonutto, 1997; di Prampero, 2000) or the use of a human centrifuge (that ESA will have available for the scientific community early next year) then counter measures will have to be developed to prevent muscle and bone wasting.

Why microgravity simulation on earth is not enough

Research on the problem has adequately defined its extent by studies of astronauts during and after spaceflight and there have been three rather clear lessons. First, the rate of loss of muscle and bone are much greater than observed during model situations on Earth (such as head down bed rest); secondly, wasting, at least of

bone, continues for some time after the return to full gravity on Earth (Rittweger *et al*. 2005) so that rehabilitation may take months to years; and thirdly, that all the counter measures which have been hitherto applied, (including a variety of Heath-Robinson contraptions involving straps, elastic cords, treadmills, bicycles, etc) have only partly mitigated, but not prevented, the losses. It appears reasonably obvious that simple muscular contractions, even those contractions which impose some force on bones and tendons, do not sufficiently to mimic the effects of loading in gravity (Alkner & Tesch, 2004; Reeves *et al*. 2005).

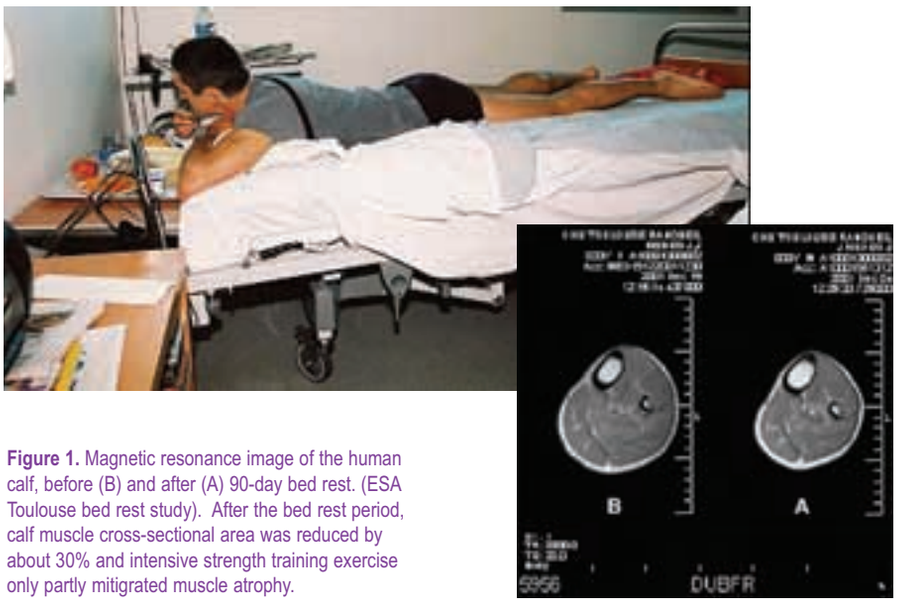


Figure 1. Magnetic resonance image of the human calf, before (B) and after (A) 90-day bed rest. (ESA Toulouse bed rest study). After the bed rest period, calf muscle cross-sectional area was reduced by about 30% and intensive strength training exercise only partly mitigated muscle atrophy.

Perhaps this is one of the reasons why studies of bed rest have yielded results sometimes in contrast with those obtained in actual microgravity. In simulated microgravity, such as bed rest, individuals are studied under highly controlled conditions and their activity levels can be closely monitored. In microgravity, accurate levels of physical activity are often not recorded or reported and physical countermeasures are prescribed by the crew surgeon with no control of the investigators (Kozlovskaya and Grigoriev, 2004). Furthermore, unlike simulated microgravity, exposure to true zero-g has been shown to directly induce a reduction in myofibrillar and connective tissue protein synthesis (Vandenburgh *et al*. 1999). This strongly suggests that there is something about gravity which has an effect even in the 6° head-down tilted position which tends to maintain musculoskeletal mass and which is missing in space. However, head-down bed rest remains the model of choice for simulating the effects of microgravity on earth.

What could we do with access to astronauts making short space visits?

If we hypothesize that there is such an entity within muscle and bone as a 'gravity sensor' then it seems plausible to suppose that this sensor is a protein which is coded for by messenger RNA produced after transcription of genes in the nucleus. The best way to identify the sensor would be by searching for gene expressions which are present in circumstances of full gravity and missing in circumstances of zero gravity when there would be an infinite step change between the two conditions. Our current evidence suggests that the anabolic influence of the gravity sensor remains reasonably strong even under conditions of bed rest and therefore in order to detect changes in gene expression we need a rapid square wave diminution/ restoration of the force of gravity with samples taken before and after. This is exactly what could be done in studies of astronauts on the International Space Station (if Britain were signed up to the programme!).

It is perfectly feasible with current technology to compare samples of muscle and bone taken from astronauts before going into space, immediately after a sojourn of say a week (which is likely to be long enough to cause the changes in gene expression) and then on their return from space and at intervals thereafter. Muscle and bone biopsies are much less invasive than generally supposed and are painless with appropriate local anaesthetic; they are without long term consequences if carried out using appropriate techniques. By comparing the expression of genes under normal gravity conditions and immediately after returning from zero gravity it ought to be possible to identify those genes likely to be involved in the sensing of gravity and the signalling of the sensory correlate to processes ultimately as controlling muscle and bone masses.

The technology is certainly available now with incredibly powerful DNA and proteomic array "labs-on-a-chip" (e.g. Albala, 2001; Chittur, 2004), and there are several precedents for gene expression experiments conducted on human space missions (e.g. Taylor *et al.* 2002; Wilson *et al.* 2002; Semov *et al*. 2002). Having identified the sensor, it ought to be possible to design ways of intervening in its actions by pharmacologically blocking or enhancing parts of the signalling pathway in order to ameliorate the effects of loss of gravitational influences on anabolic and catabolic processes in muscle and bone.

The possible benefits

Of course this does sound like science fiction - but all future scientific projections are science fiction until they become a reality. We certainly have the technical capabilities to identify the gravity sensor in the way we have described above and there are major pressures which would help encourage the pharmaceutical industry to become involved in solving the problems of which genes are transcribed their protein products and how it would enhance or diminish their influence by pharmacological means.

What do we mean by major pressures? Currently in the developed countries the increase in life expectancy which has come as a result of effective conquering of most infectious diseases and better nutrition, has caused a rapid growth in that segment of the population which is over 60. We know that muscle and bone loss occurs in this group at a rate of about 15-20% per decade beyond the age of 50 and that these musculoskeletal losses have major implications for the individual and society in terms of loss of dependence and therefore an increase in dependence upon family, neighbours and the state, but also in terms of increased medical costs due to falls and fractures. Currently there are few strategies which can be successfully applied to the problem. Presently, no effective drugs have been found yet which may fully prevent muscle loss, at best they can only mitigate but not prevent muscle atrophy and the drugs which are used to counter bone loss are sufficiently expensive than we could probably not afford to use them if all of the members of our society who were losing bone were diagnosed adequately. In any case, these drugs are relatively ineffective particularly in terms of the maintenance of bone qualities other than bone mineral density (i.e. content of calcium salts).

If we were able to identify the gravity sensor responsible for the maintenance of muscle and bone and identify ways of enhancing the action of the anabolic signalling pathways, which rationally must be associated with its action, then we could slow or prevent the massive loss of muscle and bone and the huge costs associated with this. In the United States alone the excess costs of sarcopenia alone have been calculated at about $1000 per individual per year and a similar figure is likely to be applicable within Europe. The costs of bone wasting are probably of the same order.

Thus it seems to us that studying human physiology and patho-physiology in astronauts would not only give us the chance of overcoming a major obstacle to manned space flight but would have huge potential benefits here on earth in terms of attempting to deal with the currently intractable medical and social problem of ageing of the musculoskeletal system. Although in this article we have mainly dealt with muscle and bone, similar arguments may be put forward for the other major physiological systems known to be affected by microgravity.

There are, of course, other benefits. One which we believe has been severely underplayed is the very likely halo effect for science and technology education of the human space flight programme. The topic is one which excites the interest and enthusiasm of school pupils and students something which is likely to help reverse the flight from science which we currently experience among young people.

These and other benefits for biological and biomedical and clinical science were recognised by the eminent members of the Microgravity Review Panel (Bill Wakeham, Richard Sykes, Peter Williams and Steve Garwood) set up by Lord Sainsbury, the UK's science minister, to make recommendations on Britain's possible involvement in microgravity research. Despite the positive recommendations for this part of the program (Wakeham *et al*. 2003), no positive increase in the biological aspects of space research has occurred. The UK government has effectively ignored the advice of its experts.

What about the costs?

Even though the costs of maintaining the International Space Station are considerable, the costs of carrying out the clinical research we have discussed above are marginal (e.g. the cost of the current Women International Space Simulation for Exploration (WISE) bed rest study on women totals €3.6M for all agencies) compared to the potential benefits in countering sarcopenia and osteopenia (billions of pounds), and in reversing the internal brain drain away from science. It would be a great pity if we could not grasp the present opportunity to realise these benefits for an expenditure which would be a tiny fraction of the potential return. Unfortunately in the UK we are excluded because Britain does not pay the entrance price of a fill ESA subscription and puts all its eggs into robot missions like the ill fated Beagle project. It has even proved impossible to persuade the Research Councils to ask for special collaborative status for British scientists with NASA and ESA.

Aknowledgements

We are grateful to Drs Didier Schmitt and Patrik Sunblad of ESA for their kind advice and support to this initiative.

Marco Narici[1]
Michael Rennie[2]

[1]Institute for Biophysical and Clinical Research into Human Movement, Manchester Metropolitan University, Alsager, UK

[2]Graduate Entry Medical School, University of Nottingham, City Hospital Derby, UK

References

Albala JS (2001). Array-based proteomics: the latest chip challenge. *Expert Rev Mol Diagn* **1**, 145-152.

Alkner BA & Tesch PA (2004). Knee extensor and plantar flexor muscle size and function following 90 days of bed rest with or without resistance exercise. *Eur J Appl Physiol* **93**, 294–305.

Chittur SV (2004). DNA microarrays: tools for the 21st century. *Comb Chem High Throughput Screen* **7**, 531-537.

Kozlovskaya IB & Grigoriev AI (2004). Russian system of countermeasures on board the international space station: the first results. *Acta Astronaut* **55**, 233–237.

di Prampero PE & Antonutto G (1997). Cycling in space to simulate gravity. *Int J Sports Med* **18**, S324-S326.

di Prampero PE (2000). Cycling on earth, in space, on the moon. *Eur J Appl Physiol* **82**, 345-360.

Morley JE, Baumgartner RN, Roubenoff R, Mayer J & Nair KS (2001). Sarcopenia. *J Lab Clin.Med* **137** 231-243.

Reeves ND, Maganaris CN, Ferretti G & Narici M (2005). Influence of 90-day simulated microgravity on human tendon mechanical properties and the effect of resistive countermeasures. *J Appl Physiol* **98**, 2278 - 2286.

Rittweger J, Frost HM, Schiessl H, Oshima H, Alkner B, Tesch P & Felsenberg D (2005). Muscle atrophy and bone loss after 90 days' bed rest and the effects of flywheel resistive exercise and pamidronate: results from the LTBR study. *Bone* **36**, 1019–1029.

Semov S, Semova N, Lacelle C, Marcotte R, Petroulakis E, Proestou G & Wang E (2002). Alterations in TNF- and IL-related gene expression in space-flown WI38 human fibroblasts. *FASEB J* **16**, 899-901.

Taylor WE, Bhasin S, Lalani R, Datta A & Gonzalez-Cadavid NF (2002). Alteration of gene expression profiles in skeletal muscle of rats exposed to microgravity during a spaceflight. *J Gravit Physiol* **9**, 61-70.

Vandenburgh H, Chromiak J, Shansky J, Del TM & Lemaire J (1999). Space travel directly induces skeletal muscle atrophy. *FASEB J* **13**, 1031-1038.

Wakeham B, Sykes R, Williams P, Garwood S (2003). Recommendations of the Microgravity Review Panel, http://www.microgravity.org.uk/recommendations.pdf (also available at http://www.star.ucl.ac.uk/~iac/Microgravity_Report.pdf).

Wilson JW, Ramamurthy R, Porwollik S, McCelland M, Hammond T, Allen P, Ott CM, Pierson DL & Nickerson CA (2002). Microarray analysis identifies Salmonella genes belonging to the low-shear modelled microgravity regulon. *Proc Nat Acad Sci USA* **99**, 13807-13812.

Melatonin, sleep and the biological clock

Jo Arendt cuts through the hype and looks at the genuine benefits of a 'hormone of darkness'

Humans are a diurnal species, active during the day, sleeping at night. In optimal conditions alternating light and darkness dictate the timing of our endogenous clock (the central circadian pacemaker, the suprachiasmatic nuclei or SCN) which in turn synchronises our physiology such that systems work in harmony with the environment. We sleep better when the internal clock is in the right phase. But in developed countries we live, most of us, in an artificial environment. Alarm clocks wake us up, not the sunrise. Thanks to Edison we do not go to bed at sunset. Our homes, cities and roads are illuminated and many of us (around 20% of the UK work force) work at night and attempt to sleep during the day usually at odds with internal physiology. We subject ourselves to abrupt large shifts in time cues when flying long haul. Our biology has not caught up with our technology: the clock does not adapt rapidly to night work (indeed if at all) or time zone change.

Even if people are day active the clock can drift away from its normal phase (usually by delay) with insufficient time cues. The most important of these is sufficiently bright light of suitable spectral composition (short wavelengths are most effective). This is particularly evident in the Polar winter (no sunlight at all), but may be prevalent in urban indoor workers, especially those with a strong diurnal preference for evening (owls). Delayed Sleep Phase Syndrome (DSPS) is a manifestation of extreme delay. As a result of suboptimal timing of the internal clock, at the very least we frequently get insufficient, poor quality sleep. Shift workers in particular have short sleep, taken at an inappropriate phase of the clock. At worst, living counter to the internal clock may lead to increased risk of major disease, including heart disease and cancer, and even the current obesity epidemic may be related in part to insufficient good quality sleep.

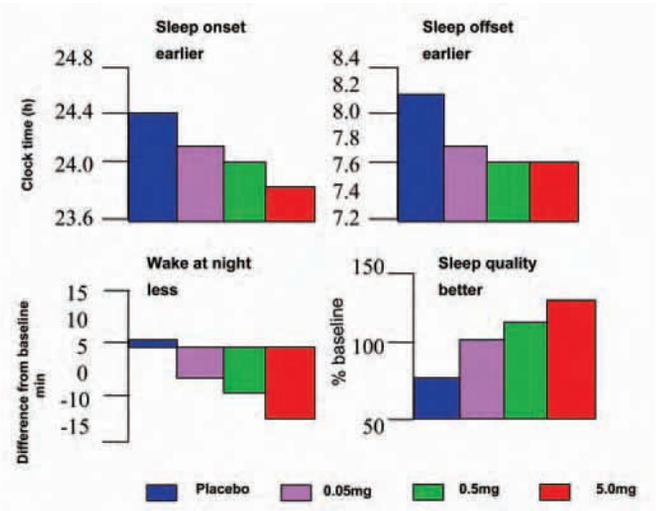
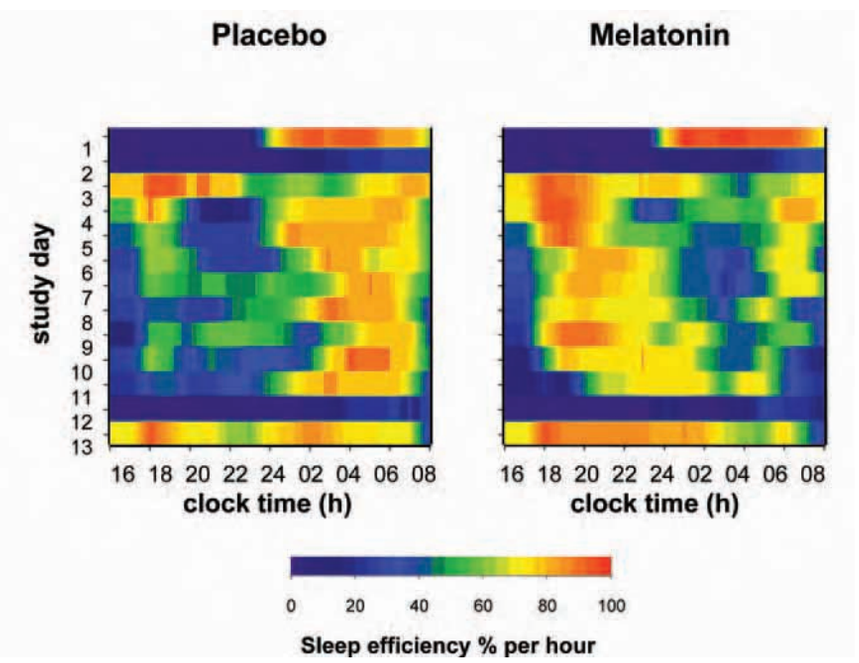


Figure 1 (above). A single melatonin treatment (fast release) at 1700 h. Red, 5mg; green, 0.5mg; violet, 0.05mg; blue, placebo (adapted from Deacon & Arendt, 1995). **Figure 2** (below). Advance and redistribution of sleep by melatonin (1.5mg surge-sustained release days 3-10) daily at 1600 h, then recumbent in near darkness until 0800 h. Sleep efficiency (% time spent asleep per unit time, polysomnography) colour scale is shown below. All measured circadian rhythms phase advanced (from Rajaratnam *et al.* 2003, 2004).



So where does the pineal hormone melatonin come in to this? Reading some of the scientific literature one might be forgiven for concluding that melatonin was the 'hormone of sleep'. It is, in fact, a 'hormone of darkness', effectively an internal time cue. It is normally made at night in all species, whether nocturnal or diurnal. Its secretion pattern reflects the length of the night and serves to define 'biological night'. Thus in humans, (but not in rats) its peak values are normally associated with sleep and the nadir of core body temperature, alertness and performance and other phenomena characteristic of night time. The rhythm is driven by the SCN and, like all circadian rhythms, its timing is dictated largely by the light dark cycle. The melatonin rhythm (or that of its major metabolite 6-sulphatoxymelatonin) is the best peripheral index of biological clock timing and is used extensively to

determine human circadian timing in health and disease.

Suppression of melatonin by light at night has provided a tool for investigation of circadian photoreception, a hypothesis for the health risks of shift work, and the rationale for the first light treatments of seasonal depression (SAD). The major physiological role of melatonin is to convey information about light and darkness: it is the only solidly established humoral method of signalling time of day and time of year to other physiological systems.

Pinealectomy abolishes the melatonin rhythm- and the ability to perceive daylength changes: a major problem for daylength dependent seasonal species. Humans retain some seasonality (even in fertility) and some of the actions of melatonin in humans can be interpreted on this basis. In physiological or near to physiological doses, it has two main effects in humans. Taken during 'biological daytime' it induces sleepiness and lowers body temperature in the hours following ingestion, if subjects are recumbent or semi-recumbent in dim light. Taken during biological afternoon-evening it facilitates sleep and advances the timing of all circadian rhythms measured to date, probably by a direct action on receptors in the SCN (Fig. 1). Taken in the biological evening in a person whose clock has drifted into a phase which is too late for optimal sleep at the conventional time, the phase advance may optimise the timing of the clock relative to the desired sleep time. It is also reported to delay the circadian system if taken during early 'biological morning' but this is more controversial. Its effects on sleep, within an extended 'sleep opportunity' (Fig. 2), suggest that it does not grossly alter sleep structure or total sleep time but redistributes sleep in a manner reminiscent of the redistribution of sleep in long and short nights in animals.

In the absence of strong time cues the circadian system desynchronises completely from 24h clock time and assumes the genetically determined endogenous period (usually longer than 24h) of the individual concerned ('free-running'). This condition is particularly common in blind people with no light perception at all. In most cases melatonin is able to synchronise such free running circadian rhythms to 24 h with suitable timing and dose (Fig. 3).

These 'chronobiotic' properties, together with its acute effects on sleep, mean that melatonin is used successfully to correct circadian rhythm abnormalities such as free-running sleep disorder of the blind, DSPS, and, less consistently, the sleep problems of jet lag and night shift work. The extensive use of melatonin as a sleep aid in, for example, the USA rests probably on the correction by evening melatonin of a tendency to delayed phase. With suitable dose and timing both the acute and phase shifting effects of melatonin can be maximised. These properties have inspired new pharmacological approaches to the treatment of health problems and it is possible that optimisation of circadian timing will have many health benefits yet to be determined.

Since melatonin has powerful physiological effects in photoperiodic species we must be certain of its uses and limitations. There is little information on long term safety even though we have known for more than 40 years that melatonin induced sleepiness (as reported by Aaron Lerner who discovered melatonin) and might be clinically useful. However, there is very little evidence in the short term for toxicity or undesirable effects in humans. Indeed there is accumulating evidence for anti-cancer properties and other potential benefits. The extraordinary 'hype' of the miraculous powers of melatonin in the recent past did a disservice to acceptance of its proven therapeutic uses.

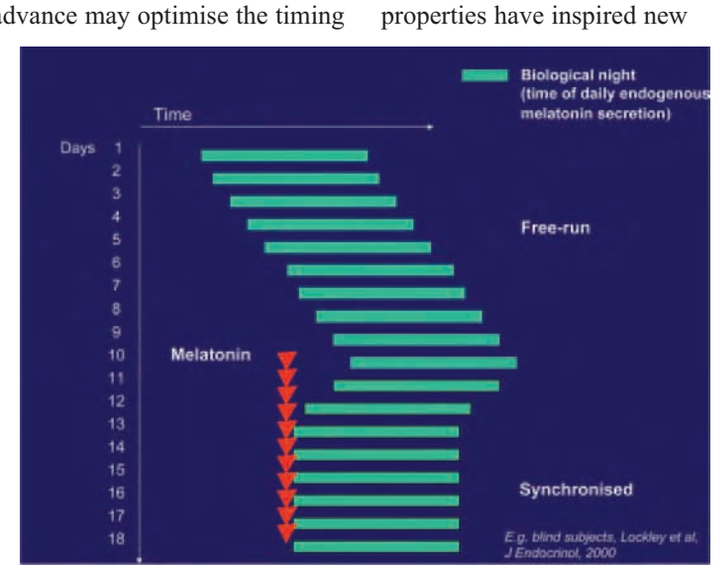


Figure 3. Diagram of the synchronisation (by advance) of 'free-running' rhythms by melatonin.

Josephine Arendt
Centre for Chronobiology, School of Biomedical and Molecular Sciences, University of Surrey, Guildford, Surrey, UK

References and further reading

Arendt J (2000). Melatonin, circadian rhythms, and sleep. Editorial. *N Engl J Med* **343**, 1114-1116.

Arendt J & Skene DJ (2004). Melatonin as a chronobiotic. *Sleep Medicine Reviews* **9**, 25-39.

Arendt J (2005). Melatonin: characteristics, concerns and prospects. *J Biol Rhythms* **20**, 291-303.

Deacon S & Arendt J (1995). Melatonin-induced temperature suppression and its acute phase-shifting effects correlate in a dose-dependent manner in humans. *Brain Res* **688**, 77-85.

Lockley SW, Skene DJ, James K, Thapan K, Wright J & Arendt J (2000). Melatonin administration can entrain the free-running circadian system of blind subjects. *J Endocrinol* **4**, R1-6 .

Rajaratnam SM & Arendt J (2001). Health in a 24-h society. *Lancet* **358**, 999-1005.

Rajaratnam S M, Dijk D J, Middleton B, Stone B & Arendt J (2003). Melatonin phase-shifts human circadian rhythms with no evidence of changes in the duration of endogenous melatonin secretion or the 24-hour production of reproductive hormones. *J Clin Endocrinol Metab* **88**, 4303-4309.

Rajaratnam SMW, Middleton B, Stone BM, Arendt J & Dijk D-J (2004). Melatonin advances the circadian timing of EEG sleep and directly facilitates sleep without altering its duration in extended sleep opportunities. *J Physiol* **561**, 339-351.

Revell VL, Arendt J, Terman M & Skene DJ (2005). Short-wavelength sensitivity of the human circadian system to phase advancing light. *J Biol Rhythms* **20**, 270-272.

Thapan K, Arendt J & Skene DJ (2001). An action spectrum for melatonin suppression: evidence for a novel non-rod, non-cone photoreceptor system in humans. *J Physiol* **535**, 261-267.

Warman VL, Dijk D-J, Warman GR, Arendt J & Skene DJ (2003). Phase advancing human circadian rhythms with short wavelength light. *Neurosci Lett* **342**, 37-40.

Short-term plasticity has a long synaptic history

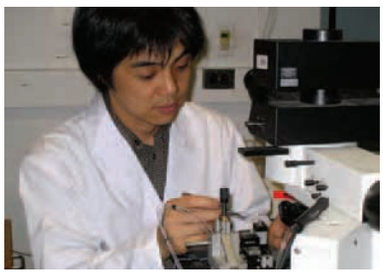
Short- and long-term synaptic plasticity are dynamically linked, and this interplay helps to increase the information storage capacity of a synapse reports Yuji Ikegaya

The rivers are running through the years, yet they are not the same water anymore.

This famous Japanese aphorism, written in the 13th century by the classical essayist Chomei Kamono, means that the rivers stay put in appearance but their material content (or inner state) is different. New data indicates that this principle holds true for synaptic transmission in the brain.

Synaptic efficacy is dynamic. For instance, when closely spaced action potentials reach a presynaptic terminal, the synapse does not transmit them identically to a postsynaptic neuron. This form of synaptic plasticity, termed short-term plasticity, is diverse (Fig. 1). At facilitating synapses, the postsynaptic responses to later spikes in repetitive presynaptic firing are larger than that to the first one, whereas at depressing synapses, they are smaller. Whether a synapse is facilitating or depressing depends upon the type of synapse. Hippocampal mossy fibre-CA3 synapses and climbing fiber-Purkinje cell synapses are typically facilitating, whereas parallel fiber-Purkinje cell synapses display depression. However, the biophysical mechanisms underlying short-term plasticity are multiple and complex, and therefore in many types of synapses, including hippocampal Schaffer collateral-CA1 synapses, these two forms of plasticity, i.e., facilitation and depression, often coexist, resulting in complicated profiles of short-term plasticity.

In addition to short-term plasticity, central synapses often show long-term plasticity, that is they are capable of increasing or decreasing their efficacy of transmission in response to brief repetitive synaptic activation and thereafter maintaining the changed efficacy for a long time. The temporal pattern of synaptic stimulation determines whether synaptic efficacy is strengthened (long-term potentiation,



Yuji Ikegaya

LTP) or weakened (long-term depression, LTD). Long-term plasticity represents long-lasting 'memory' at the sub-neuronal level and is widely believed to underlie learning and memory at the behavioural level.

Interestingly, the induction of long-term plasticity influences the profile of short-term plasticity. This interplay between two forms of synaptic plasticity is called redistribution of synaptic efficacy (RSE). The induction of LTP and LTD causes an increase and decrease in the depressing properties of synapses, respectively (Markram & Tsodyks, 1996; Sjöström et al. 2003). For an extreme example of LTP at neocortical synapses, short-term depression is augmented to a point at which the elevated synaptic efficacy disappears in later responses to high-frequency presynaptic firing (Markram & Tsodyks, 1996). Therefore, LTP and LTD do not simply amplify or attenuate synaptic transmission but rather transform (or filter) the content of information conveyed by spike discharges.

Strangely, however, RSE seems to be absent in hippocampal synapses (Pananceau et al. 1998; Selig et al. 1999; Buonomano, 1999). At these synapses, LTP is likely to equally increase all sequential responses to repetitive presynaptic stimulation, i.e., no change in the degree or direction of short-term plasticity. It has been unclear whether this apparent discrepancy is due to the difference in brain regions or stimulation protocols for LTP induction. Our new data now indicate that the latter is the case (Yasui et al. 2005).

Using hippocampal slice preparations, we confirmed the previous findings that at Schaffer collateral-CA1 synapses, LTP was not accompanied by RSE. But this was true only if tetanic stimuli

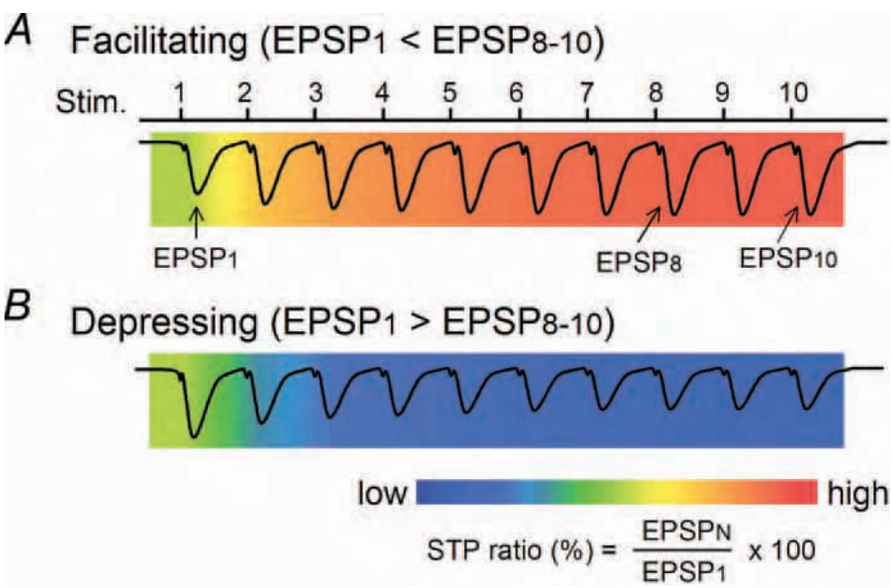


Figure 1. Two types of short-term plasticity (STP): facilitating synapses (*A*) and depressing synapses (*B*). Short-term plasticity of a synapse is quantifiable with a STP ratio, which is calculated from the equation indicated below the panel *B*. Wave represents consecutive excitatory postsynaptic potentials (EPSPs) evoked by a 10-pulse train at 40 Hz and is merged with a pseudocolor-scale image of STP ratios. EPSPN indicates the slope of the Nth EPSP response in 10 successive train stimuli.

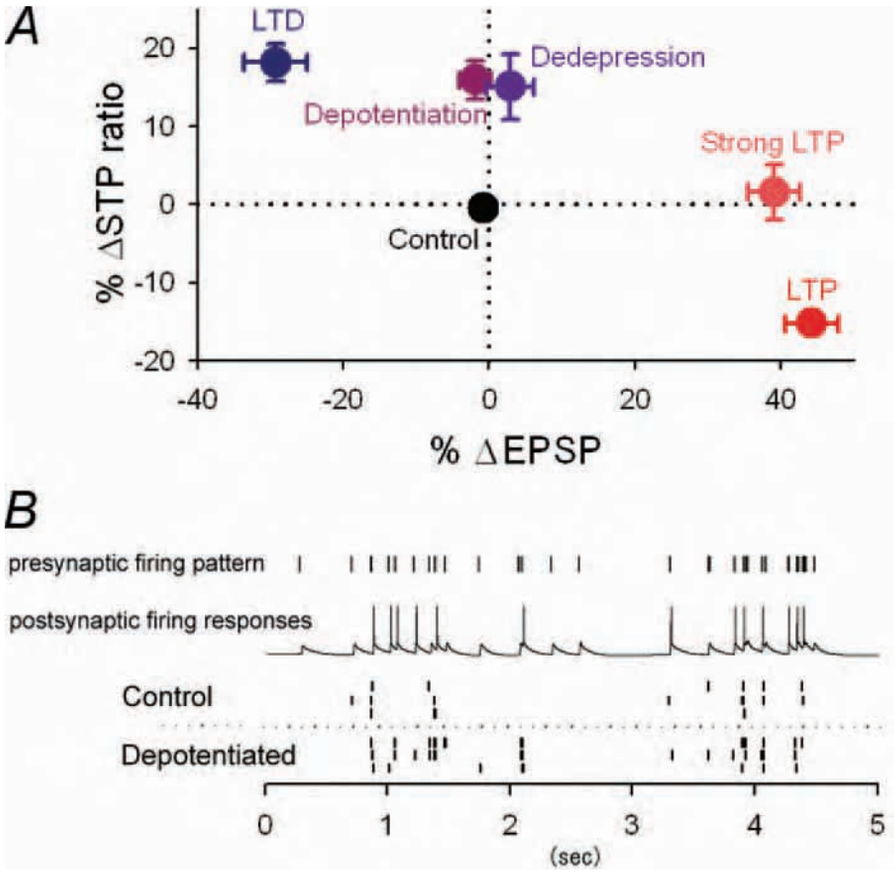


Figure 2. Synaptic states are separable by EPSP and short-term plasticity (STP). (*A*) Various forms of synaptic plasticity and their RSE. Different synaptic states were plotted at different points in the space of changes in the initial synaptic response ($EPSP_1$) and STP ratios of $EPSP_{8\text{-}10}$. Note that RSE is defined as a change in the STP ratio after induction of synaptic plasticity (%ΔSTP ratio). For details, see Fig. 1. Data indicate that the history of synaptic activity is encoded in the forms of $EPSP_1$ and STP. (*B*) RSE modifies a frequency preference in spike responses. Top: an example of spiking activity generated by a CA1 pyramidal cell in response to a stimulus train with a natural temporal pattern sampled from a CA3 pyramidal cell in a free-moving rat. Bottom: rasterplots of postsynaptic spike timings 20 min before and 30 min after the induction of depotentiation. Firing responses are slightly, but significantly (as assessed by information theory), different between control and depotentiated synapses.

strong enough to induce saturated LTP were repeated four times. When the same tetanic stimulation was applied once, RSE was evident, that is, depressing synapses became more depressing after the LTP induction (Fig. 2A). Because LTP was already saturated by one tetanus under our experimental conditions, the synaptic efficacy for the initial spike in burst firing was no more changed by additional three tetani. This means that the states of these synapses that experienced one and four tetani are distinguishable only by RSE, i.e. the degree of short-term plasticity. Thus, synapses with apparently saturated LTP are still capable of encoding information by changing their profile of short-term plasticity. In this respect, we emphasize that RSE extends the information storage capacity of a synapse.

Similar phenomena take place after reversal of LTP (depotentiation) and LTD (dedepression) (Fig. 2A). Synapses potentiated by tetanic stimulation are believed to return to the basal conditions, i.e. the pre-tetanus state, by receiving subsequent low-frequency stimulation. We found that such 'depotentiated' synapses were still accompanied by RSE although apparent synaptic strength, monitored by single-pulse stimulation, readily came back to baseline. Thus, depotentiation only ostensibly erases LTP, but the depotentiated synapses continue to convey information about the past plasticity, representing a unique functional state that differs from either naïve states or LTP, i.e., another level of plasticity. In fact, depotentiated synapses responded differently froma natural pattern of presynaptic activity, as compared with control synapses (Fig. 2B).

We thus conclude that short-term plasticity at central synapses is highly dynamic and could serve as a historic record of synaptic plasticity. This predicts a novel syntax of circuit operations, i.e. state-dependent propagations of neural signals. Elucidating RSE would reveal the computational significance of synaptic modifications.

Yuji Ikegaya
Laboratory of Chemical Pharmacology, Graduate School of Pharmaceutical Sciences, University of Tokyo, Japan

References

Buonomano DV (1999). Distinct functional types of associative long-term potentiation in neocortical and hippocampal pyramidal neurons. *J Neurosci* **19,** 6748-6754.

Markram H & Tsodyks M (1996). Redistribution of synaptic efficacy between neocortical pyramidal neurons. *Nature* **382,** 807-810.

Pananceau M, Chen H & Gustafsson B (1998). Short-term facilitation evoked during brief afferent tetani is not altered by long-term potentiation in the guinea-pig hippocampal CA1 region. *J Physiol (Lond)* **508,** 503-514.

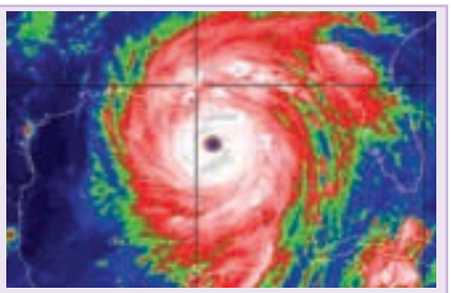
Selig DK, Nicoll RA & Malenka RC (1999). Hippocampal long-term potentiation preserves the fidelity of postsynaptic responses to presynaptic bursts. *J Neurosci* **19,** 1236-1246.

Sjöström PJ, Turrigiano GG & Nelson SB (2003). Neocortical LTD via coincident activation of presynaptic NMDA and cannabinoid receptors. *Neuron* **39,** 641-654.

Yasui T, Fujisawa S, Tsukamoto M, Matsuki N & Ikegaya Y (2005). Dynamic synapses as archives of synaptic history: State-dependent redistribution of synaptic efficacy in the rat hippocampal CA1. *J Physiol (Lond)* **566,**143-160.

Hurricane Katrina

In the light of the devastating damage and loss of life caused by Hurricane Katrina in the USA in August, and in its aftermath, The Physiological Society extends its deepest sympathy to Members, colleagues and their families who have been affected in any way by the disaster.



Intestinal adaptation to fasting: to live at any price

Caroline Habold

Animals in their natural habitat can survive prolonged periods of fasting: up to 4 months for the emperor penguin, one to several months for pythons, and several weeks for mammals during the cold season. In the early 1980s, Goodman *et al.* and Le Maho *et al.* showed that whole body metabolism was not constant throughout a long fast, and could be divided into three differing phases: the short phase I, characterized by the exhaustion of glycogen stores; phase II, defined by the use of lipid reserves for energy expenditure; and the late phase III, marked by an increasing protein catabolism. Even if these changes are accompanied by a severe atrophy of digestive organs, animals can re-feed successfully whatever the duration of the fasting period was, and rebuild their body reserves. What are the mechanisms permitting intestinal absorption after fasting? Are some nutrients preferably absorbed rather than others? Does whole body metabolism interfere?

Commonly, expression of intestinal hexose transporters increases with the concentration of sugar in the intestinal lumen. However, an increase in glucose absorption has been observed after 'short' periods of fasting i.e. corresponding to phase I or II, when the amount of glucose transporters in the enterocyte membrane should be lowered. This could be explained by an increase in membrane permeability – or even by more sodium/glucose cotransporters (SGLT1) in the apical membrane – and/or by a decrease in intracellular sodium concentration triggering glucose transport via SGLT1. The increase in the density of SGLT1 in the enterocyte apical membrane has, however, not been confirmed by other studies (for review, see Ferraris & Carey, 2000). Fructose absorption via the apical transporter GLUT5 has been shown to increase after a short fast. In contrast, the basolateral transporter GLUT2 involved in hexose release to the blood stream should not be affected by caloric restriction.

In our recent study (Habold *et al.* 2005), we clearly showed a difference in the expression of SGLT1 according to the metabolic and hormonal state reached by fasting rats. This effect could explain the previous differing findings. As there is no difference in the amount of SGLT1 protein and mRNA between normally fed and phase II fasting rats, we observed a significant increase from these values during the longer fasting phase III. After having perfused the small intestine with a glucose solution, we observed a significant increase in glucose absorption in phase III but also a slight one in phase II fasting rats that do not show an increase in SGLT1 transporters. This last result suggested that glucose may also cross the small intestine epithelium via a paracellular route due to an increase in epithelial permeability upon fasting. Unlike SGLT1, the facilitative apical GLUT5 and basolateral GLUT2 are down-regulated throughout fasting whatever the phase is.

If GLUT2 is absent from the enterocyte basolateral membrane, how can the glucose entering in the cell at the apical pole via SGLT1, be released to the blood stream during fasting? By studying intestinal gluconeogenesis, according to the availability in gluconeogenic precursors, i.e. glycerol in phase II and amino acids in phase III fasting, we measured an increase in the gene expression, protein level and activity of the glucose-6 phosphatase (Glc6Pase) during phase III. We hypothesized that this enzyme could then be involved not only in endogenous glucose production during the fast, but also in the release of glucose to the blood stream as described by Stumpel *et al*. (2001) in

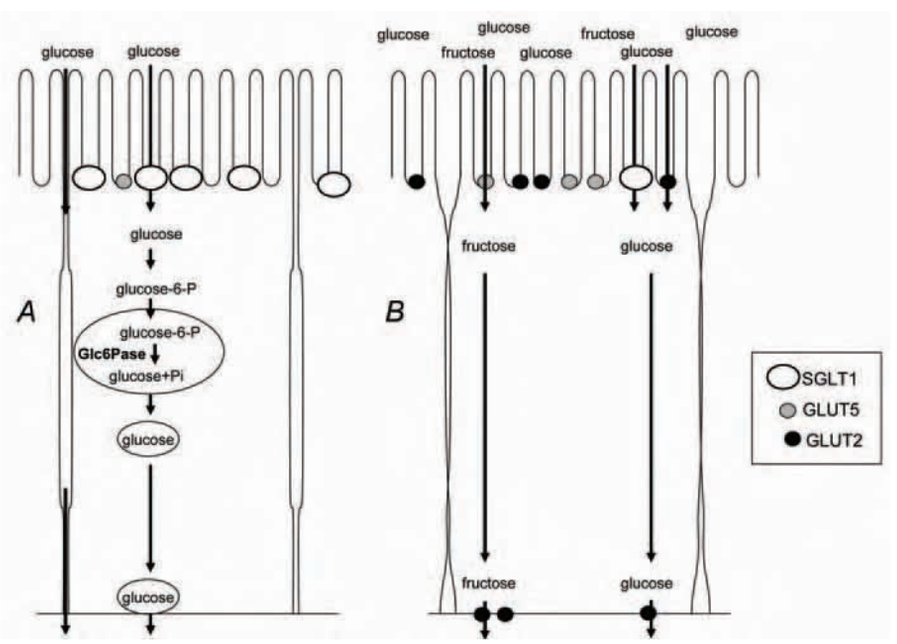


Figure 1. Proposed mechanism for glucose transepithelial transport after a few minutes refeeding following a phase III fast (*A*) and after 2 h re-feeding following this phase (*B*). Immediately after food ingestion, glucose may be absorbed *via* paracellular and transcellular ways. The transcellular way involves apical transport of glucose through SGLT1 and baso-lateral release *via* a mechanism involving Glc6Pase. Refeeding then induces an increase in GLUTs transporters in the apical membrane and therefore, massive absorption of fructose and glucose.

the absence of the baso-lateral transporter GLUT2. According to this study, glucose absorbed via SGLT1 is phosphorylated to glucose-6 phosphate before entering the endoplasmic reticulum where it is hydrolyzed by Glc6Pase to glucose and phosphate. Glucose then re-enters the cytosol and diffuses out of the enterocytes by a membrane traffic pathway. So, during the late phase III of fasting, the increase in SGLT1 and Glc6Pase should permit the rapid absorption of glucose even at low concentration when food is restored (Fig. 1*A*). Interestingly, at this stage, animals in natural conditions as well as laboratory rats show an increase in locomotor activity consistent with a 'search for food' behaviour.

Re-feeding following either a phase II or a phase III fast stimulates the gene and protein expressions of GLUT5 and GLUT2. Furthermore, we observed that, after only 2 hours re-feeding, GLUT2 was mainly located at the apical membrane (Fig. 2). Recruitment of GLUT2 to the brush border membrane involves a protein kinase C pathway activated by glucose absorption *via* SGLT1 (Kellett, 2001) and can then permit absorption of glucose at high concentrations (Fig. 1*B*).

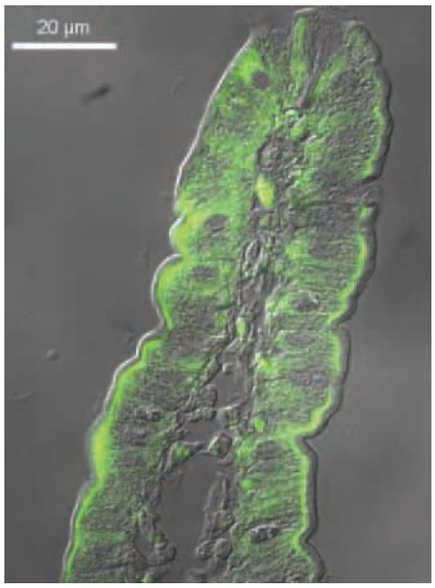


Figure 2. GLUT2 immunolocalization after 2h refeeding following a phase III fast.

The unaltered and even increased absorption capabilities of the intestine during the critical phase III fast, when the animal reaches a critical threshold in nutrient reserves, coincides with a 'search for food' activity and could permit food assimilation immediately after re-feeding. This could thus be a survival mechanism, an ultimate energy expenditure before death in case of food becomes available.

In summary, the metabolic and hormonal status of fasted animals modifies the expression of intestinal hexose transporters, but further research is required to describe other transporters and to answer the question of whether some key nutrients may be preferentially absorbed depending on the fasting phase. This would bring new perspectives in the re-nutrition of patients suffering from severe mal-nutrition associated with, for example, anorexia nervosa or cancer cachexia.

Caroline Habold
CNRS, CEPE, Strasbourg, France

References

Ferraris RP, Carey HV (2000). Intestinal transport during fasting and malnutrition. *Annu Rev Nutr* **20**, 195-219.

Goodman MN, Larsen PR, Kaplan MN, Aoki TT, Young VR & Ruderman NB (1980). Starvation in the rat. II Effect of age and obesity on protein sparing and fuel metabolism. *Am J Physiol* **239**, E277-E286.

Habold C, Foltzer-Jourdainne C, Le Maho Y, Lignot JH & Oudart H (2005). Intestinal gluconeogenesis and glucose transport according to body fuel availability in rats. *J Physiol* **566**, 575-586.

Kellett GL (2001). The facilitated component of intestinal glucose absorption. *J Physiol* **531**, 585-595.

Le Maho Y, Vu Van Kha H, Koubi H, Dewasmes G, Girard J, Ferre P & Cagnard M (1981). Body composition, energy expenditure, and plasma metabolites in long-term fasting geese. *Am J Physiol* **41**, E342-E354.

Stumpel F, Burcelin R, Jungermann K & Thorens B (2001). Normal kinetics of intestinal glucose absorption in the absence of GLUT2: evidence for a transport pathway requiring glucose phosphorylation and transfer into the endoplasmic reticulum. *Proc Natl Acad Sci USA* **25**, 11330-11335.

Then ... and now

Roger Thomas and Enrico Stefani (pictured top left as post-docs in the Biophysics Department of UCL in 1968) were together again, below left, at The Society's Oxford Focused Meeting in September 2005.

Roger (left) and Stefano were photographed at the Oxford dinner by Ligia Toro.

See also Roger's article *How I came to probe intracellular pH and realised it can be interesting* which appeared in a recent issue of the magazine (*Physiology News* **60**, 5).

Benevolent Fund

Many thanks to all those who took part in the Benevolent Fund raffle at the Bristol Meeting – we raised a grand total of £330.42. The lucky winner was Jan Mares from the Czech Republic who won a Fortnum & Mason food hamper.

The Fund has already given out £4,700 in grants this year so support is vital if we are to sustain this level of grant-making.

If you would like more information about the Fund, or would like to make a donation or set up regular giving, please contact Elfa Wilmot in The Physiological Society's London Administration Office (ewilmot@physoc.org)

The tongue does not the taste system make

The taste system responds to diverse chemical stimuli that affect not only taste receptors on the tongue, but also taste receptors on the palate. Despite the highly complex nature of taste stimuli and the many sites of receptor activation, the brain appears to code the tastes of food and fluid in a relatively stable manner

One of the most fundamental, but least scientifically understood, of the sensory systems is taste. The taste system helps to guide each of us toward food and fluid selection vital to important regulatory functions such as energy maintenance, hormonal status and electrolyte balance. Taste perception is the product of a multifaceted and complex sensory system. When foods and fluids are consumed, they generally enter the front of the mouth, move throughout the oral cavity, and proceed to the back of the mouth prior to swallowing. Contact time with any particular area of the mouth is variable, dependent upon the texture or content of the ingested substance. Throughout the oral cavity are taste receptor cells, clustered into groupings of taste buds and subserved by four taste nerves. Although regional specializations exist across the oral cavity, each of the nerves conducts multiple sensitivities corresponding to the various classes of chemical stimuli. Ultimately, tastes must be coded in the brain as reliably corresponding to each particular food or fluid via the integration of this complex information.

Suzanne Sollars

A closer examination of individual regional differences and similarities in the oral cavity further demonstrates the difficult task of understanding how the brain ultimately codes the array of information received from taste receptor cells. For example, in humans taste buds are spread across the tongue, but they are also present on the soft palate, a region in the back part of the oral cavity on the roof of the mouth. While we know quite a lot about taste buds on the tongue, much less information is available about taste receptors on the palate. The presence of these taste buds can easily be demonstrated by application of a small amount of salt water or sugar water to the soft palate. With the head tilted backward, apply one of the solutions to the posterior palate with an eyedropper, taking care to avoid getting solution onto the tongue. The majority of those who participate in this demonstration report tasting both the salt and the sugar solutions when contact occurs on the palate alone. Furthermore, after closing the mouth and tasting the solutions on the tongue, participants invariably report a qualitatively different taste than when the solution was on the palate alone. While these reported differences in taste perception are merely anecdotal evidence, they suggest some sort of differential processing of taste perception on the tongue versus the palate.

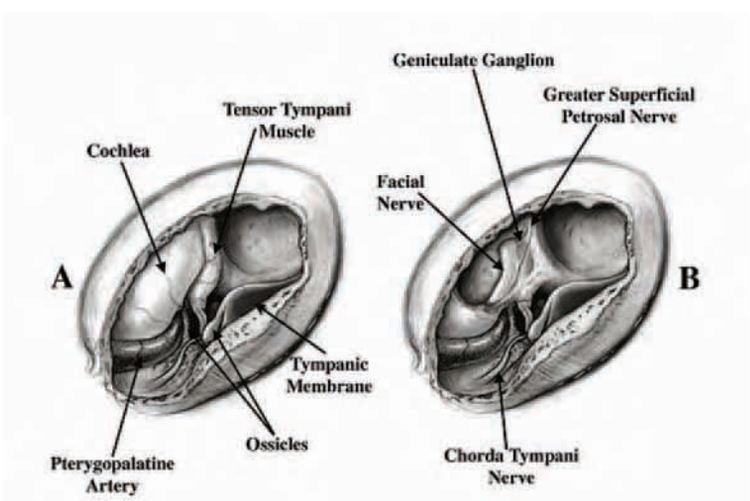


Figure 1. Illustration of the geniculate ganglion in the rat which is the site of cell bodies for both the chorda tympani nerve (innervating taste buds on the anterior tongue) and the greater superficial petrosal nerve (innervating taste buds on the palate). The surgical approach to the ganglion is through the neck. After locating a bony mass next to the ear called the tympanic bulla, the upper surface of the bulla is opened to reveal the cochlea and the ossicles of the auditory system. The cochlea and other bone must be removed in order to visualize the geniculate ganglion.

To better understand the coding of taste stimuli, the rodent model is widely used in taste experiments to obtain data on the electrophysiological processing of chemical stimuli. In the rat, taste buds are found across the tongue and palate in areas similar to those in humans. However, taste buds on the palate have a wider distribution in the rat than in the human. Rats' taste buds are distributed in a region directly behind the incisor teeth called the nasoincisor duct, in a region called the geschmacksstreifen (German for 'taste stripe'), and also on the soft palate which is directly behind the geschmacksstreifen. The greater superficial petrosal nerve (GSP) innervates each of these areas, with cell bodies contained within the geniculate ganglion (Fig. 1). Early experiments on the electrophysiological properties of the GSP indicated a higher sensitivity of this nerve to sucrose than observed in other taste nerves (Nejad, 1986). Subsequent experiments have also shown strong neural responses to other stimuli, such as salt (Sollars & Hill, 1998). In a recent experiment (Sollars & Hill, 2005), we demonstrated that only a subset of individual nerve fibres respond strongly

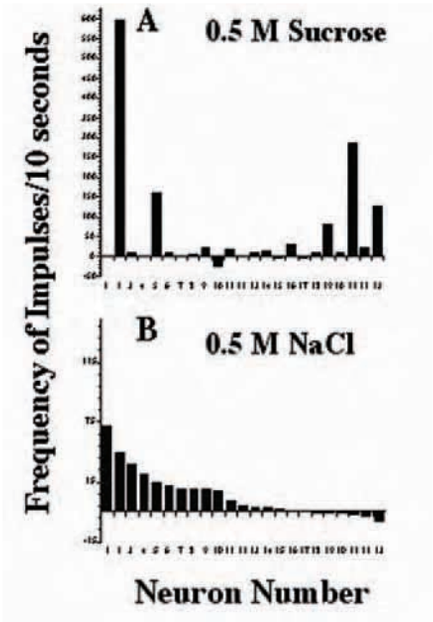


Figure 2. Example of the electrophysiological responses to sodium chloride and sucrose by individual neurones located in the geniculate ganglion (M = molar concentrations). These particular neurones innervated palatal taste receptors. The "Frequency of Impulses/10 seconds" reflects the number of action potentials produced by the stimulus within a 10-second time frame immediately after stimulus onset. Note the difference in the y-axis scale between 'A' and 'B'. The "neuron number" corresponds to a particular cell. Thus, neuron 1 in 'A' is also neuron 1 in 'B' and so on. This graph demonstrates the response differences of individual cells to taste stimuli and the differences in the pattern of responses across stimuli. To see the responses of these cells to other types of stimuli, refer to Sollars & Hill, 2005.

to sucrose, while some do not respond at all to this stimulus (Fig. 2). Other fibres are more responsive to salt, quinine, or acid. Fibres of the other taste nerves are also differentially responsive to various stimuli, yet the pattern and strength of particular chemical responses varies between the nerves (Frank, 1991; Lundy & Contreras, 1999; Sollars & Hill, 2005).

Therein lies a small example of the complicated dynamics of taste sensory coding. Multiple receptor subtypes, continual receptor cell turnover, potential temporal coding based on stimulus contact time or location of receptors in the oral cavity, and variability in neural representation across nerves come together to form a relatively stable interpretation of chemical stimulus representation in the cortex. The 'taste map' is yet to be determined, but with each nuance of recent advances in the field, we come ever closer to a better understanding of what makes this system so complex.

Suzanne I Sollars
Department of Psychology, University of Nebraska Omaha, Omaha, NE, USA

References

Frank ME (1991). Taste-responsive neurons of the glossopharyngeal nerve of the rat. *J Neurophysiol* **65**, 1452–1463.

Lundy RF Jr & Contreras RJ (1999). Gustatory neuron types in rat geniculate ganglion. *J Neurophysiol* **82**, 2970–2988.

Nejad MS (1986). The neural activities of the greater superficial petrosal nerve of the rat in response to chemical stimulation of the palate. *Chem Senses* **11**, 283–293.

Sollars SI & Hill DL (1998). Taste responses in the greater superficial petrosal nerve: substantial sodium salt and amiloride sensitivities demonstrated in two rat strains. *Behav Neurosci* **112**, 991–1000.

Sollars SI & Hill DL (2005). *In vivo* recordings from rat geniculate ganglia: taste response properties of individual greater superficial petrosal and chorda tympani neurones. *J Physiol* **564.3**, 877–893.

Muscle Contraction Special Interest Group

Since the reforms in the format of The Physiological Society Meetings, there have been two Muscle Contraction Special Interest Group (SIG) sessions. The first was at the King's College London Meeting from 17-20 December 2004, where a total of nine oral and three poster presentations were given. The topics varied from examination of myosin isoforms in humans with malocclusions to determination of muscle mRNA levels in response to lipopolysaccharide. Two memories stick in my mind, first the cold in the lecture hall, which presumably accounted for the limited audience and, in contrast, the packed poster session probably assisted by the warmth and the mulled wine. An interesting and well-attended research symposium on cell signalling in striated muscle was also organised by Jonathan Kentish independently of the Muscle Contraction SIG – a painless and easy way to get updated about the current status of regulatory molecules in a variety of contractile tissues.

The second session was in Bristol, where the joint meeting of The Physiological Society and FEPS ran between 20-23 July 2005. An inspiring symposium on ionic contributions to muscle fatigue was organised by Torben Clausen and the conclusion was that involvement, or not, of a specific ion depended very much on the way in which fatigue was induced. The dedicated Muscle Contraction session started immediately after this and there was a total of seven oral and two poster presentations. A very interesting talk by Aurelio Pimenta from University of Sao Paulo describing a possible neural modulation of citrate synthase was my highlight of the day. A respectable turnout with lots of questions from the audience.

For those planing to attend only one meeting next year, the following might be of interest. A focused one day meeting funded in part by The Physiological Society on the control and modification of excitation-contraction coupling in healthy and diseased muscle will be held at the University of Heidelberg, Germany on 13 September 2006 immediately after the annual meeting of the European Society of Muscle Research. Further details will be announced later.

Joseph Bruton
Convenor, Muscle Contraction SIG
(joseph.bruton@kei.se)

International Workshops

Three International Workshops, aimed primarily at young physiologists from Eastern Europe and the Third World are planned for 2006:

19-25 March (Caracas, Venezuela)
Membrane transport in health and disease
http://www.physoc.org/international/

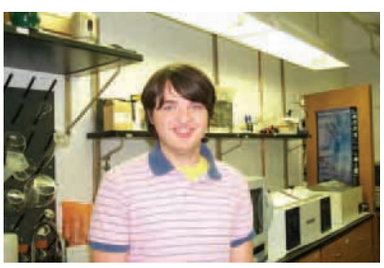
4-7 June (Kiev, Ukraine)
The study of nociception from periphery to brainstem
http://www.physoc.org/international/

21-23 September (Prague)
Lung function in health and disease
http://www.physoc.org/international/

For more details contact Helen Close, The Society's International Administrator (hclose@physoc.org)

Integrity and vulnerability of skeletal muscle innervation in ageing mammals

Skeletal muscle weakness in ageing mammals may result from factors affecting the neural control of muscle structure and function. Muscle denervation is relentless and a more extensive process than previously believed. Partially denervated muscle cells, recently described in senescent mice, might contribute to muscle weakness in ageing mammals



Osvaldo Delbono (top) and Robert Guerring

As a human reaches old age it is common to observe a general decrease in muscle mass and a proportionate decrease in muscle force and power. Both of these effects can lead to an impairment of daily living activities, morbidity, disability, and mortality and decreased life expectancy. The mechanisms by which these losses occur are only partially understood and are the subject of much scientific investigation.

Muscle weakness in ageing mammals may result from factors affecting the neural control of muscle structure and function, directly from changes in the intrinsic properties of the muscle, or a combination of both (for a review see Delbono, 2003). One neural factor, denervation, has been shown to increase with age. Denervation is the loss of muscle innervation and results in atrophy and loss of muscle fibres. The graduated disconnection of muscle fibres from their spinal cord motoneuron ultimately affects the entire muscle, causing a decreased force-generating capacity and a smaller muscle mass.

Studies of spinal cord motoneuron and muscle fibre counting, together with electrophysiological motor unit and muscle functional recordings, indicate that denervation slowly evolves over decades. The process of muscle denervation occurs concurrently with reinnervation, whereby some denervated fibres become reinnervated by axonal sprouting of neighbouring healthy and slow-type motor units. Reinnervation apparently remodels motor units and is characterized by a resulting higher proportion of slow-type fibres (Larsson *et al.* 1993). The effect of these innervation changes is a concomitant increase or decrease in the number of fibres in muscle motor units. As this dynamic process progresses a reduction in muscle strength takes place when muscle fibers are partially denervated, or when denervation outpaces reinnervation and the absolute number of contracting fibres decreases (Fig. 1). A decline in muscle specific force occurs before a significant decline in muscle fibre number and suggests that impaired motoneuron function may have a deleterious effect on the intrinsic fibre capacity to develop force. Innervation, therefore, is vital to the survival of muscle fibres. Due to the aforementioned consequences of denervation it is important to know the extent and quality of this process in ageing muscle.

Several studies have reported skeletal muscle denervation and reinnervation, as well as motor unit remodeling in ageing rodents or humans (for a review see Payne & Delbono, 2004). Accurate measurement of denervation has remained elusive due to technical difficulties in functionally and histochemically assessing the expression of molecules that appear with denervation.

To investigate this issue, Wang and coworkers explored the expression of the sodium channel Na_v 1.5 as an index of denervation (Wang *et al.* 2005). Electrophysiological and immunohistochemical assays were performed in a short muscle of the mouse paw, flexor digitorum brevis (FDB), which provides an excellent model preparation for functional recordings (Fig. 2). The use of the potent and specific toxin tetrodotoxin (TTX) allowed the researchers to discriminate between cells expressing

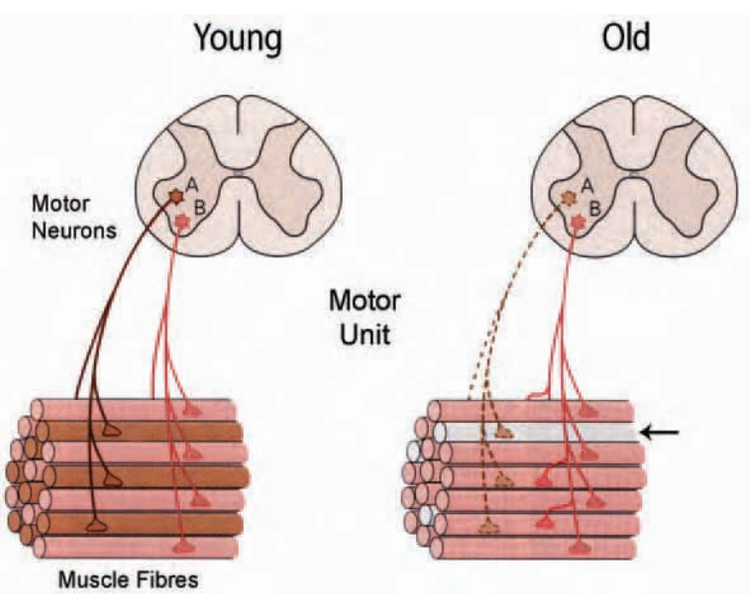


Figure 1. Schematic representation of motor unit remodeling and denervation in old mammals. (Adapted from Kandel *et al. Principles of Neural Science* 4th edition, p. 695. McGraw Hill)

Na_v 1.5 (TTX-resistant, denervated) or Na_v 1.4 (TTX-sensitive, innervated) channels. Three populations of fibres were found in old mice:

(a) innervated, corresponding to 50% of all the fibres recorded and exhibiting high sensitivity to TTX;
(b) denervated, representing 13% of the fibres and exhibiting a significant resistance to TTX; and
(c) partially denervated, composed of 35% of the fibres that exhibited a sensitivity to TTX intermediate between the previous two groups.

These experiments were complemented by the detection of denervated fibres in histological sections of the FDB muscle exposed to specific and purified antibody against Na_v 1.5. About half of the fibres from old mice were positive for the $Na_v1.5$ antibody, compared to less than 2% of fibres from young animals, providing further evidence for greater denervation in ageing muscle than was previously estimated. In summary, this study detected the presence of a significant fraction of partially denervated fibres that, together with the small fraction of fully denervated fibres, add up almost 50% of the FDB fibres recorded at late stages of life. Taken together, partially and fully denervated fibres, represent about half of all fibres tested in the FDB muscle of old mice in this study. Literature values have ranged between 25 and 50% loss in human spinal cord motoneuron and motor units with age (for a review see (Lexell, 1997)).

Whether differences in magnitude or extent of denervation among species and muscle subtypes exist is not known at the present time. The neural cell adhesion molecule (NCAM) has been used as a marker of denervation in other studies. Approximately 10% of extensor digitorum longus muscle fibres of aging rats have been reported denervated using immunohistochemistry for NCAM (Urbanchek *et al.* 2001). This number likely corresponds to the highest denervated/most TTX-resistant fibres observed in the study reported above.

Two important questions remain:

(1) Are the fibres which exhibit intermediate sensitivity to TTX capable of developing force? and
(2) Is the FDB muscle more susceptible to denervation than other hindlimb muscles?

Though a fertile area for continued investigation, we can expect that fibres depicting an intermediate response to TTX are at different stages of denervation in ageing rodents. A significant fraction of those fibres may be electrically excitable both directly and indirectly, through the nerve, and still contribute somewhat to the loss in muscle force with ageing. The location of the FDB in the plantar aspect of the paw can render this muscle more susceptible to trauma than the remaining hindlimb muscles. Muscle and nerve mechanical trauma, in association with impaired repair during ageing, could be the propitious territory for a relentless denervation process.

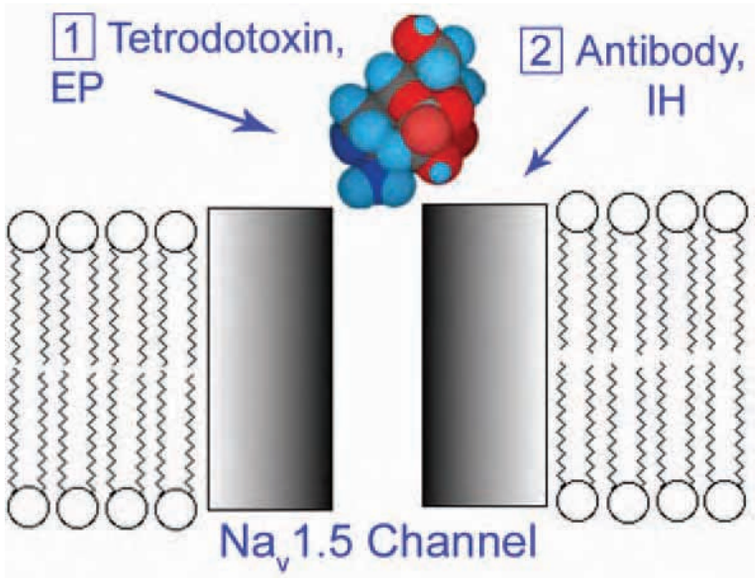


Figure 2. Diagram of the TTX-resistant sodium channel ($Na_v1.5$) and the two strategies applied to investigate denervation in ageing muscle: (1) electrophysiology (EP) and (2) immunohistochemistry (IH), using TTX and $Na_v1.5$ antibody, respectively (Adapted from the University of Maryland Chemical Ecology webpage).

Acknowledgements

The preparation of this manuscript and the studies from laboratory reported here were supported by grants from the National Instituted of Health/National Institute on Ageing (AG18755, AG13934 and AG15820) to Osvaldo Delbono. We are greatful to Gregory Piccola for editing this manuscript.

Robert Guerring[1]
Osvaldo Delbono[1,2,3]

[1]Department of Physiology and Pharmacology, [2]Department of Internal Medicine, Section on Gerontology and [3]Neuroscience Program, Wake Forest University School of Medicine, Winston-Salem, NC, USA

References

Delbono O (2003). Neural control of aging skeletal muscle. *Aging Cell* **2,** 21-29.

Larsson L, Biral D, Campione M & Schiaffino S (1993). An age-related type IIB to IIX myosin heavy chain switching in rat skeletal muscle. *Acta Physiol Scand* **147,** 227-234.

Lexell J (1997). Evidence for nervous system degeneration with advancing age. *J Nutr* **127,** 1011S-1013S.

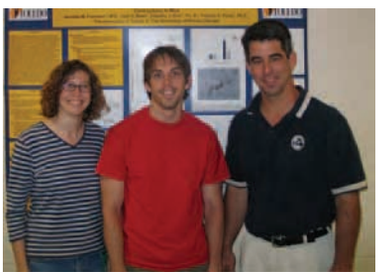
Payne AM & Delbono O (2004). Neurogenesis of excitation-contraction uncoupling in aging skeletal muscle. *Exerc Sport Sci Rev* **32,** 36-40.

Urbanchek MG, Picken EB, Kalliainen LK . & Kuzon WM Jr (2001). Specific force deficit in skeletal muscles of old rats is partially explained by the existence of denervated muscle fibers. *J Gerontol A Biol Sci Med Sci* **56,** B191-197.

Wang ZM, Zheng Z, Messi ML & Delbono O (2005). Extension and magnitude of denervation in skeletal muscle from ageing mice. *J Physiol* **565,** 757-764.

Interplay between neutrophils and skeletal muscle after exercise. What's going on?

Neutrophils appear in skeletal muscle after exercise. The mechanisms by which skeletal muscle activates neutrophils and the function of neutrophils in skeletal muscle are, write Francis Pizza and colleagues, beginning to be revealed



Above (left to right): Jennifer Peterson, Joel Baas and Francis Pizza Left: Timothy Koh

Exercise causes subpopulations of leukocytes, namely neutrophils and macrophages, to accumulate in skeletal muscle. Interestingly, neutrophils appear in skeletal muscle in the hours to days after both non-injurious exercise (e.g. stretching) and exercise-induced muscle injury (e.g. lifting weights for the first time) (Best *et al*. 1999; Pizza *et al*. 2002; McLoughlin *et al*. 2003a). Little is known about how exercise orchestrates neutrophil responses (e.g. migration, reactive oxygen species (ROS) production, and release of cytokines) and how these responses influence the physiology and plasticity of skeletal muscle.

We propose that the microenvironment of skeletal muscle after exercise dictates when and how many neutrophils appear in skeletal muscle, which products they produce, and their function in skeletal muscle (Fig. 1). In our working model, exercise causes molecular, cellular, and tissue changes in skeletal muscle that take place on an injury continuum. At the beginning of the continuum, no overt signs of muscle injury (functional impairment and histological disruptions) are apparent; whereas moderate to severe injury produces overt injury. In the different regions of the continuum there are overlapping as well as discrete cues that cause neutrophils to have different functions in injured and non-injured skeletal muscle after exercise.

Although skeletal muscle contains several cell types (e.g. skeletal muscle cells, endothelial cells, fibroblasts, and resident macrophages) that are capable of producing factors that influence neutrophil responses, evidence from our laboratory indicates that skeletal muscle cells are an important source factors that promote neutrophil migration (chemotaxis) after exercise (Tsivitse *et al*. 2005). Our experiments have demonstrated that neutrophil chemotaxis in vitro and muscle neutrophil concentrations in vivo are greater after injurious relative to non-injurious exercise (Pizza *et al*. 2002; Tsivitse *et al*. 2005). Thus, injured skeletal muscle cells may release a greater concentration of neutrophil chemoattractants or a different set of chemoattractants relative to non-injured skeletal muscle cells after exercise.

Neutrophil chemotaxis after injury could be enhanced by the release of chemotactic cytokines from neutrophils (e.g. ELR + CXC chemokines) that have invaded the injured muscle.

Once neutrophils have entered injured skeletal muscle they are thought to contribute to the removal of damaged or necrotic tissue via phagocytosis. A prerequisite for phagocytosis, however, is that neutrophils encounter factors in the milieu of injured muscle that triggers the production and release of the weaponry responsible for degrading damaged or necrotic tissue (e.g. ROS production and release of proteases). Findings from our laboratory indicate that the soluble environment of injured skeletal muscle cells contains factors that both enhance (i.e. primers) and that directly increase (i.e. activators) ROS production from neutrophils (Tsivitse *et al*. 2005). A negative consequence of neutrophil-derived ROS is that their release into the extracellular fluid may cause 'collateral damage' (secondary

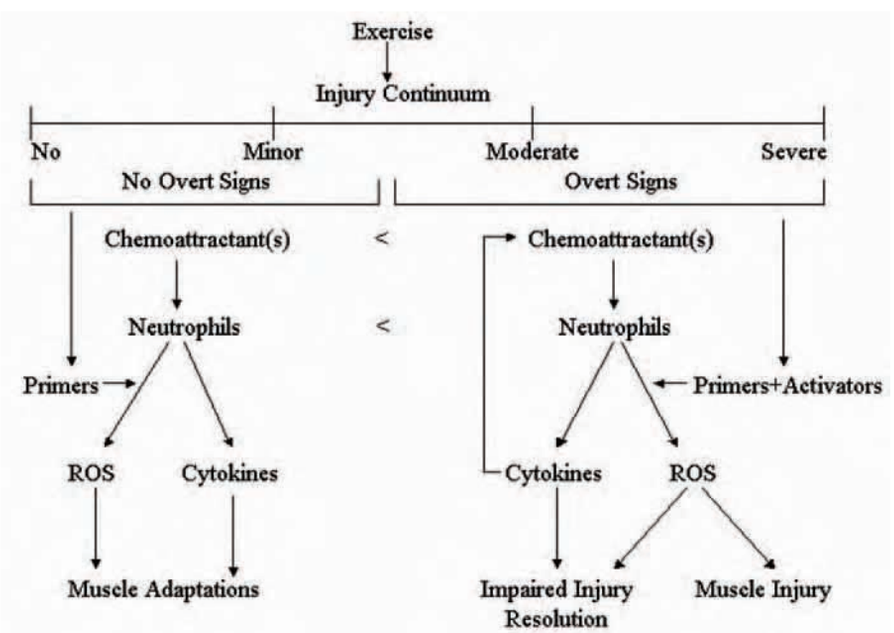


Figure 1. A working model that proposes that neutrophils have dichotomous actions in skeletal muscle after exercise. The foundational element of the model is that the environment of skeletal muscle after exercise dictates when and how many neutrophils appear in skeletal muscle, which products they produce, and their function in skeletal muscle after exercise.

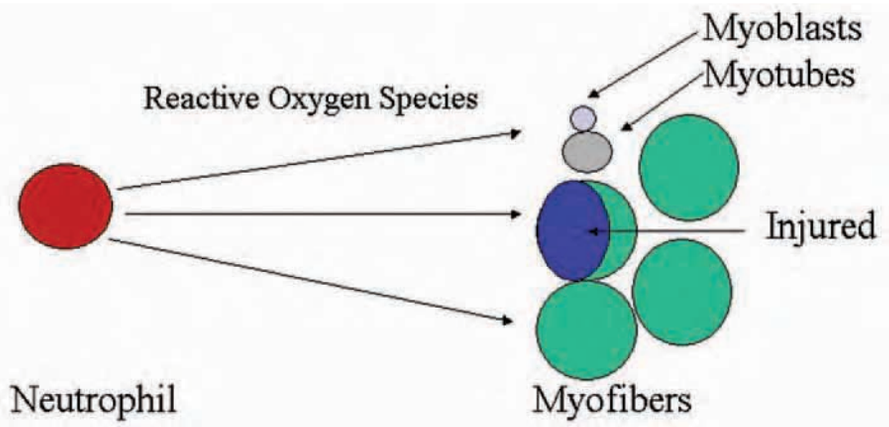


Figure 2. We propose that neutrophils cause 'collateral damage' (secondary injury) by damaging healthy regions of injured fibres and/or adjacent uninjured fibres via the release of ROS into the extracellular fluid. Neutrophils could also impair the resolution of the injury by damaging and/or impairing the growth of immature skeletal muscle cells (myoblast and/or myotubes).

injury) by damaging healthy regions of injured fibres and/or adjacent uninjured fibres (Fig. 2). We have provided support for this contention by demonstrating that neutrophils cause muscle dysfunction, histological abnormalities, and oxidative modification to skeletal muscle proteins in vivo after injurious exercise and by demonstrating the neutrophils injure cultured skeletal muscle cells via mechanisms that are dependent on neutrophil adhesion and ROS production (Pizza *et al*. 2001; McLoughlin *et al*. 2003b; Pizza *et al*. 2005).

We speculated that neutrophil-mediated injury was a necessary consequence for restoring structure and function to injured skeletal muscle. We thought it might be analogous to a home improvement project where structurally sound aspects of a construction site are often removed/damaged to optimize the restoration process. To our surprise, we found that neutrophils impaired some of the events associated with restoring structure and function to injured skeletal muscle (Pizza *et al*. 2005). The mechanism by which neutrophils impaired the resolution of the injury remains to be determined. Neutrophils may impair the resolution of exercise-induced muscle injury by damaging developing skeletal muscle cells (myoblasts and/or myotubes) (Pizza *et al*. 2001; McLoughlin *et al*. 2003b) and/or by releasing cytokines (e.g. TGF-β1, TNF-α, IFN-γ, and IL-1β) that inhibit the growth of skeletal muscle cells and/or that promote skeletal muscle protein catabolism (Hawke & Garry, 2001).

Following non-injurious exercise we found that the microenvironment of skeletal muscle cells after non-injurious exercise also contain primers, but not activators, for neutrophil-derived ROS. Because non-injured muscle presumably does not contain targets for phagocytosis, primed neutrophils in non-injured muscle after exercise may release low levels of ROS. If true, then low concentrations of ROS released from neutrophils in non-injured muscle may contribute to exercise-induced skeletal muscle adaptations by influencing redox-sensitive genes. Furthermore, because neutrophils can release cytokines in the absence of phagocytosis, neutrophil-derived cytokines may serve as cellular signals for muscle adaptations after exercise. Such adaptations may include, protection from subsequent injury, muscle growth (hypertrophy), and angiogenesis.

Further work is required to test the central elements of our working model and to reveal the mechanisms for the complex interplay between neutrophils in skeletal muscle after exercise.

Once mechanisms for the interplay have been exposed, therapeutic and/or pharmacological strategies could be developed to manipulate the inflammation biology of skeletal muscle to minimize any negative consequences of neutrophils in skeletal muscle.

Francis X Pizza[1]
Jennifer M Peterson[1]
Joel H Baas[1]
Timothy J Koh[2]

[1] Department of Kinesiology, The University of Toledo, Toledo, OH, USA
[2] School of Kinesiology, University of Illinois, Chicago, IL, USA

References

Best TM, Fiebig R, Corr DT, Brickson S & Ji L (1999). Free radical activity, antioxidant enzyme, and glutathione changes with muscle stretch injury in rabbits. *J Appl Physiol* **87**, 74-82.

Hawke TJ & Garry DJ (2001). Myogenic satellite cells: physiology to molecular biology. *J Appl Physiol* **91**, 534-551.

McLoughlin TJ, Mylona E, Hornberger TA, Esser KA & Pizza FX (2003a). Inflammatory cells in rat skeletal muscle are elevated after electrically stimulated contractions. *J Appl Physiol* **94**, 876-882.

McLoughlin TJ, Tsivitse SK, Edwards JA, Aiken BA & Pizza FX (2003b). Deferoxamine reduces and nitric oxide synthase inhibition increases neutrophil-mediated myotube injury. *Cell Tissue Res* **313**, 313-319.

Pizza FX, Koh TJ, McGregor SJ & Brooks SV (2002). Muscle inflammatory cells after passive stretches, isometric contractions, and lengthening contractions. *J Appl Physiol* **92**, 1873-1878.

Pizza FX, McLoughlin TJ, McGregor SJ, Calomeni, EP & Gunning, WT (2001). Neutrophils injure cultured skeletal myotubes. *Am J Physiol Cell Physiol* **281**, C335-341.

Pizza FX, Peterson JM, Baas JH & Koh TJ (2005). Neutrophils contribute to muscle injury and impair its resolution after lengthening contractions in mice. *J Physiol* **562**, 899-913.

Tsivitse SK, Mylona E, Peterson JM, Gunning WT & Pizza FX (2005). Mechanical loading and injury induce human myotubes to release neutrophil chemoattractants. *Am J Physiol Cell Physiol* **288**, C721-729.

Proceedings of The Physiological Society

At the Annual General Meeting of The Physiological Society, held in Bristol in July, it was agreed that the Proceedings from Society Meetings should no longer be published as part of *The Journal of Physiology*.

The Proceedings will continue to be published on The Society's website and will remain citable.

http://www.physoc.org/publications/proceedings/

Glucocorticoid regulation of blood brain barrier permeability

Homeostasis of the central nervous system (CNS) microenvironment is essential for its normal function. In the early l900s researchers found the first evidence that the brain had a specialized barrier that protected its cells. Dyes injected into the body's blood supply would stain the tissues of most organs - but not the brain. It is now known that a 'blood-brain barrier' (BBB) keeps many substances out of the brain. The walls of the vessels (endothelial cells) that carry blood into the brain form the barrier.

'Crew' members from the left: Malgorzata Burek, Christine Silwedel, Carola Förster, Nina Harke, Detlev Drenckhahn and Kinga Blecharz

The main structures responsible for this barrier property are the tight junctions (TJ). Tight junctions (occluding junctions) are cell-cell junctions that seal adjacent endothelial cells of the BBB together, preventing the passage of most ions and hydrophilic macromolecules from one side of the endothelial sheet to the other. Cadherin-based adherens junctions in close proximity are important for mechanical stabilisation of the TJ (Fig. 1). TJ are strongly developed in endothelial cells of the blood brain barrier (BBB) but only moderately formed between endothelial cells of the peripheral vasculature: leaky blood vessels in the body allow many molecules to cross through to tissue, but the tight construction of the vessels in the CNS guards against brain entry. BBB-forming brain capillary endothelial cells (BCECs) express the TJ proteins occludin and claudin-5 (Rubin & Staddon, 1999)

Many diseases of the CNS, such as stroke, brain tumours, traumatic injury or multiple sclerosis, are typically accompanied by dysfunction of the BBB. Therapeutic strategies for several of these diseases include treatment with glucocorticoids (GC) (Engelhardt, 2000) but the molecular basis of how GC regulate BBB permeability is not well understood. GCs are routinely administered for the management of the effects of stroke and brain edema. Clinical reports further describe the barrier closing effects of GCs on MRI gadolinium enhancement in acute demyelinating lesions, a marker of active blood-brain barrier damage secondary to an inflammatory process (Burnham *et al.* 1991). Complementary to this, plenty of data have been accumulated on the barrier tightening effects of GCs in *in vitro* systems of the BBB (for review see Rubin & Staddon, 1999).

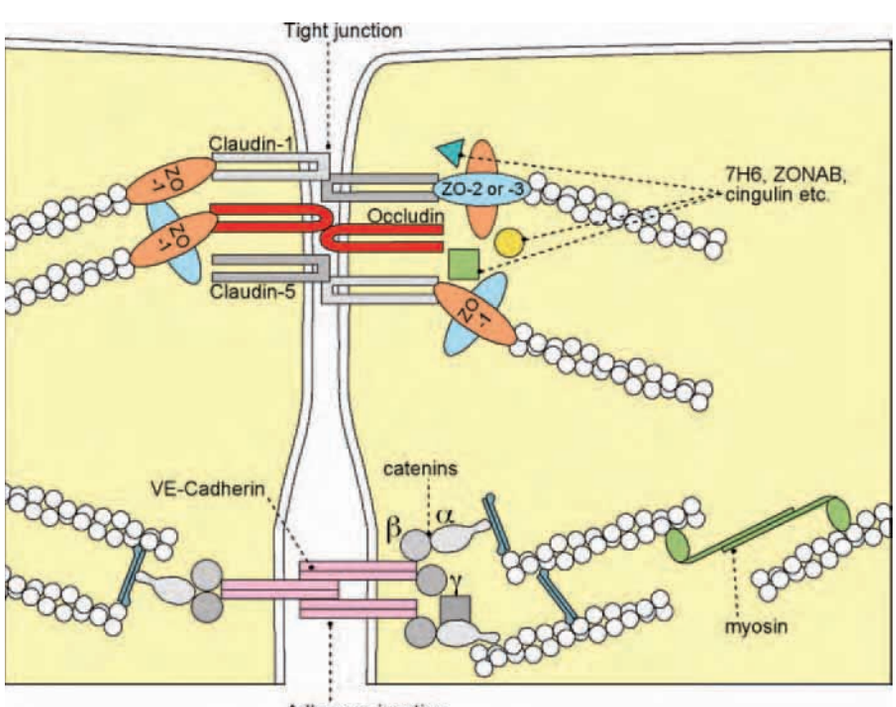


Figure 1. Tight junctions forming the paracellular seal of the BBB

It is known that GC effects are mediated by a member of the superfamily of nuclear hormone receptors, the glucocorticoid receptor (GR). These proteins influence gene expression via the activation or repression, respectively, of a given gene (Beato, 1989). Thus, the GR acts as a transcriptional regulator. The GR response elements are DNA sequences of the promoter (transcription regulatory element) of a given target gene that serve as binding sites for the GC-activated GR. The identification of GR target genes, and thus elucidation

of the underlying molecular mechanisms leading to GC-mediated BBB improvement, was hampered in the past by the lack of a genetically defined *in vitro* system, which would be easy and reproduceable to handle and allow for genetic manipulation. Research thus far has been largely limited to primary cultured BCECs from rat, bovine or porcine origin or immortalised rat brain endothelial cells and thus did not allow for dissection of molecular events. Consequently, no direct target genes for the GR could be identified, so that only indirect mechanisms influencing gene expression have been discussed in detail (Engelhardt, 2000).

Recently, the establishment of a murine immortalised BCEC cell culture system (cEND) which is responsive to GC has allowed the identification of target genes of the GR in BCECs. Administration of GCs at physiological concentrations led to an elevated expression of occludin protein and lower permeability in cEND BCECs. Transactivation of the human occludin promoter by the GR in the presence of GCs could be demonstrated in vitro using a luciferase-coupled promoter-reporter construct. These observations led to our understanding that GCs increase barrier properties of BCECs by inducing enhanced expression of the TJ transmembrane component occludin via binding of the activated GR to putative GC responsive elements (GRE) in the occludin promoter (Fig. 2) (Förster *et al.*, 2005).

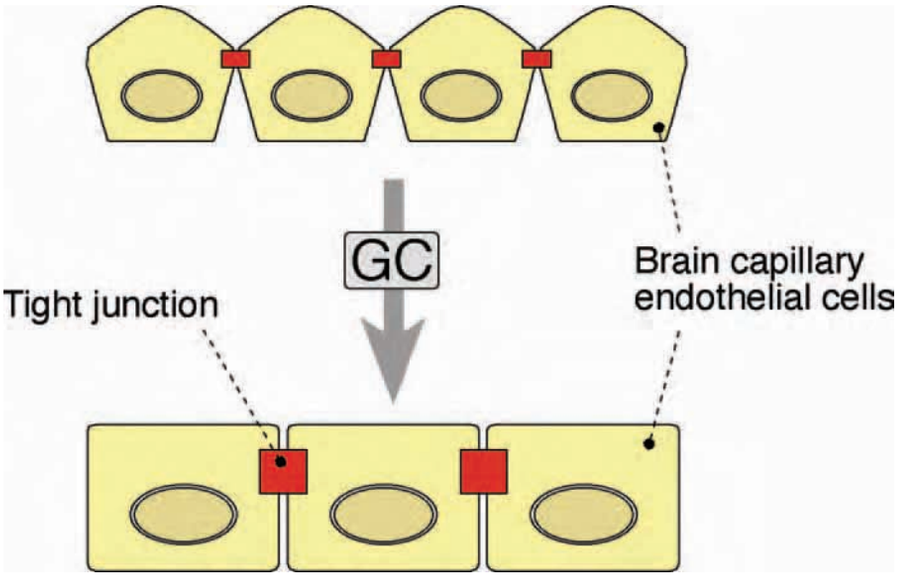


Figure 2. GCs regulate permeability of the BBB by upregulation of occludin gene expression.

Long-term treatment with high levels of GCs causes a range of severe side effects, such as weight gain concomitant with fat redistribution (Cushing syndrome), GC-induced hypertension, hyperglycemia (diabetes mellitus) and osteoporosis (Kimberly, 1991). Further dissection of the molecular events regulating gene transcription at the BBB should therefore be beneficial for the future development of target cell-specific GR ligands, ultimately as a therapeutic strategy.

Carola Förster
Institute of Anatomy and Cell Biology, University of Würzburg, Koellikerstrasse 6, D-97070 Würzburg, Germany

References

Beato M (1989). Gene regulation by steroid hormones. *Cell* **56,** 335-344.

Burnham JA, Wright RR, Dreisbach J & Murray RS (1991). The effect of high-dose steroids on MRI gadolinium enhancement in acute demyelinating lesions. *Neurology* **41,** 1349-1354.

Engelhardt B (2000). Role of glucocorticoids on T cell recruitment across the blood-brain barrier. *Z Rheumatol* **59 Suppl 2,** II/18-21.

Förster C, Silwedel C, Golenhofen N, Burek M, Kietz S, Mankertz J & Drenckhahn D (2005). Occludin as direct target for glucocorticoid-induced improvement of blood brain-barrier properties in a murine in vitro system. *J Physiol* **565(Pt 2),** 475-486.

Kimberly RP (1991). Mechanisms of action, dosage schedules, and side effects of steroid therapy. *Curr Opin Rheumatol* **3,** 373-379.

Rubin LL & Staddon JM (1999). The cell biology of the blood-brain barrier. *Annu Rev Neurosci* **22,** 11-28.

Acta Physiologica

Acta Physiologica is now the official journal of the Federation of European Physiological Societies (FEPS). Agreements have been reached with the publisher, Blackwell Publishing, that all individual members of every European Physiological Society will have free electronic access to all papers published in the journal.

A link has been established via the website of FEPS (www.feps.org). To access the journal a username and password are required.

The username and password of the National Physiological Society of the UK and RoI are:

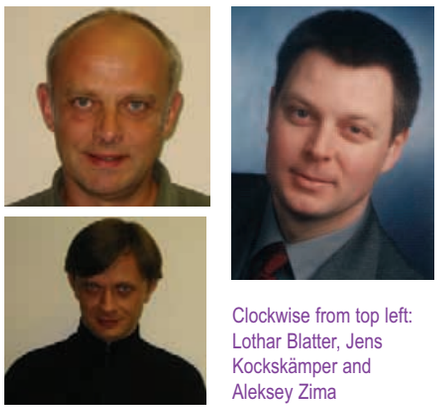
username: FEPSIU
password: IU25

2005 Nobel Prize in Physiology or Medicine

The 2005 Nobel Prize in Physiology or Medicine went to the Australians Barry Marshall (below, left) and Robin Warren (below, right) 'for their discovery of the bacterium *Helicobacter pylori* and its role in gastritis and peptic ulcer disease'.

We hope to carry a commentary in the next issue of *Physiology News*.

Glycolysis has many ways to regulate cardiac function



Clockwise from top left: Lothar Blatter, Jens Kockskämper and Aleksey Zima

During every single heart beat each individual cardiac muscle cell consumes substantial amounts of energy in form of ATP. ATP is used for calcium cycling, control of membrane potential and ultimately force development and contraction. At physiological oxygen levels cardiac cells derive 90% or more of the their energy needs from ATP production by mitochondria through oxidative phosphorylation, i.e. less than one tenth of the overall ATP production stems from the glycolytic conversion of glucose to pyruvate and lactate. Nonetheless, glycolysis has been shown to be critical for normal cardiac excitation-contraction coupling (ECC; the sequence of events that links the action potential to Ca release from the sarcoplasmic reticulum (SR) and to muscle contraction). Inhibition of aerobic glycolysis can cause depression of cardiac excitability and action potential-dependent Ca transients, changes in diastolic $[Ca]_i$, and can lead to Ca alternans in cardiac tissue (Fig. 1) (Kockskamper *et al*. 2005).

The last of these is of particular interest from a pathophysiological point of view because Ca alternans has been identified as a potentially arrhythmogenic abnormality of cardiac Ca signaling (Euler, 1999). Ca alternans is characterized by beat-to-beat alternating large and small amplitude Ca transients, concomitant with electromechanical alternans (i.e. beat-to-beat alternations of action potential duration and contraction amplitude). These (sub)cellular phenomena have their clinical equivalents in the form of changes of the electrocardiogram (manifesting e.g. as T-wave alternans or long QT syndrome) or pulsus alternans. These clinically well-documented alterations of the ECG are due to a dispersion of repolarization between different regions of the heart which can lead to unidirectional conduction blocks that can result in re-entrant arrhythmias with potentially lethal consequences for the patient. Despite its pathophysiological and clinical significance, the cellular mechanisms underlying various forms of cardiac alternans are in many aspects still only marginally understood. Evidence, however, is growing that the key to the understanding of cardiac alternans lies in the regulation of cellular energy metabolism and SR Ca release. Recent studies have provided evidence that metabolic inhibition (Huser *et al*. 2000; Kockskamper & Blatter, 2002) generates conditions that significantly enhance the propensity for Ca and electromechanical alternans. In this context, glycolysis appears to play a central role. As demonstrated recently for atrial tissue, inhibition of glycolysis caused profound Ca alternans with complex subcellular spatio-temporal features, and increased the occurrence of arrhythmogenic Ca waves (Kockskamper & Blatter, 2002).

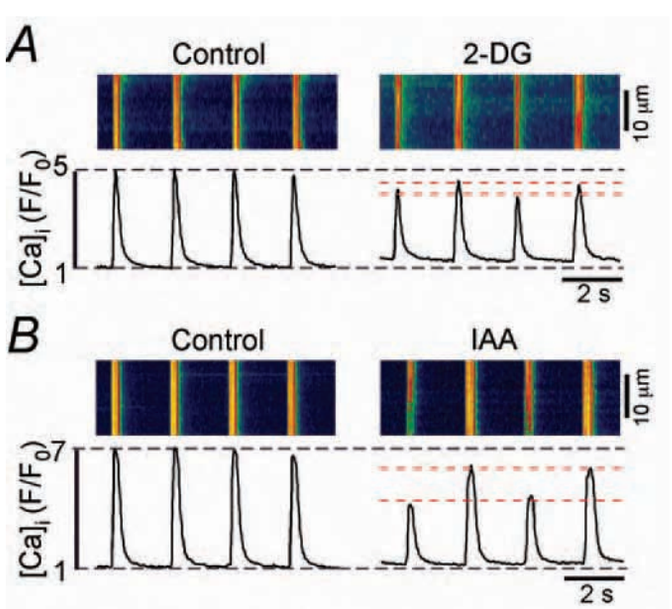


Figure 1. Effects of glycolytic inhibitors on electrically evoked Ca transients in atrial myocytes. Confocal linescan images (fluo-4 fluorescence) and corresponding whole-cell Ca transients (F/F0 plots) recorded from cat atrial myocytes. Glycolysis was inhibited with 2-deoxy-D-glucose (2-DG, 10 mM; panel A) or iodoacetic acid (IAA, 1 mM; panel B). 2-DG or IAA treatment increased diastolic [Ca]i, induced Ca alternans (red dashed lines) and decreased the amplitude of the Ca transient.

While a functional link between cellular energy metabolism and SR Ca release during ECC seems obvious, it has remained an intriguing question how glycolysis in particular, while providing quantitatively only a small contribution to the overall cellular energy metabolism, can have such profound effects on cardiac performance. For quite some time now this apparent discrepancy has led to the suggestion that glycolytically-derived ATP may serve as a preferential fuel to maintain, or at least modulate, ion transport pathways. Key glycolytic enzymes have been shown to associate with sarcolemmal and sarcoplasmic reticular membranes and functionally couple to ion transport pathways such as the sarcolemmal K_{ATP} channel, voltage-gated Ca channels, the Na/K pump, the Na/H exchange mechanism and the SR Ca pump (SERCA; for references see Kockskamper et al. 2005). The structural and functional prerequisite that would allow the preferential use of glycolytically-derived ATP over ATP generated by oxidative phosphorylation could reside

in a functional microcompartment in which ATP-dependent transporters and channels are tightly regulated by the activity of co-localized glycolytic enzymes, kinases and phosphatases (Goldhaber, 1997). The organization of these enzymes and target proteins into functional complexes (or 'metabolons') would allow for self-contained microcompartments in which proteins such as the SR Ca release channel are regulated by locally generated ATP, either directly or through phosphorylation reactions. Indeed, the notion of metabolic microcompartments is not unique to muscle and has also been demonstrated in neurons (for discussion see Huser *et al*. 2000). Thus the formation of discrete cytosolic microcompartments controlled by localized glycolytic ATP formation may represent a general scheme for the regulation of a number of cellular processes.

Recent experimental evidence has added an additional layer of complexity in the regulation and modulation of SR Ca release by glycolysis. A number of studies (see Kockskamper *et al*. 2005) have demonstrated that glycolysis affects SR function and SR Ca release not only through generation of ATP but also through direct interactions of glycolytic intermediates and products with the Ca release channel (also known as ryanodine receptor, RyR) itself.

For example (Fig. 2), recording of single channel activity of RyRs incorporated into lipid bilayers revealed that the intermediate of glycolysis fructose-1,6-bisphosphate (FBP) significantly increased, whereas the glycolytic product pyruvate decreased, the open probability of the RyR. Consistent with these findings, spontaneous SR elementary Ca release events (Ca sparks) recorded from atrial myocytes were facilitated by FBP and inhibited by pyruvate.

The current state of our knowledge clearly indicates that modulation of ECC by glycolysis is highly complex. The RyR, the key player responsible for Ca release, is regulated by a number of modulators (ATP, NAD^+/NADH, pH, glycolytic intermediates and products) which are directly influenced by glycolytic activity. Thus, any perturbation eliciting only subtle changes of glycolytic flux may, in principle, affect SR Ca release and ECC. At any given time the balance between local changes of stimulatory and inhibitory modulators of the RyR will determine the changes of its open probability.

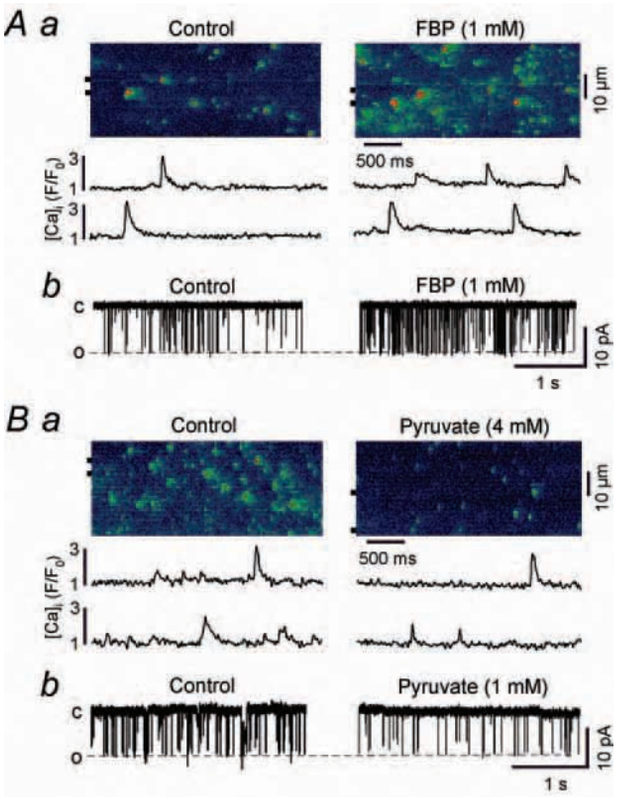


Figure 2. Modulation of ryanodine receptor (RyR) activity by intermediates and products of glycolysis. A, Effect of fructose-1,6-bisphosphate (FBP) on Ca spark activity (Aa) and single channel activity (Ab). B, Effect of pyruvate on Ca spark activity (Ba) and single channel activity (Bb). FBP increased RyR activity and pyruvate decreased RyR activity.

This becomes particularly evident in acute and chronic cardiac disease states. During acute ischemia, for example, the concentrations of inhibitors of RyR activity rise dramatically (L-lactate, H^+, NADH, Mg) whereas, at the same time, the concentrations of stimulators of RyR activity decrease (ATP, NAD^+). The overall result will be a decreased activity of the RyR contributing to the suppression of Ca transients during ischemia. In heart failure, transporters and enzymes involved in glycolysis are downregulated (reviewed in Ventura-Clapier *et al*. 2004) suggesting that altered glycolytic flux may also contribute to abnormal Ca handling and release in the failing heart.

Acknowledgement

This research was supported by NIH R01 HL62331.

Lothar A Blatter[1]
Jens Kockskämper[2]
Aleksey V Zima[1]

[1] Department of Physiology, Loyola University Chicago, Maywood, IL, USA

[2] present address: Abteilung Kardiologie und Pneumologie, Georg-August-Universität, Göttingen, Germany

References

Euler DE (1999). Cardiac alternans: mechanisms and pathophysiological significance. *Cardiovasc Res* **42,** 583-590.

Goldhaber JI (1997). Metabolism in normal and ischemic myocardium. In *The Myocardium*, 2nd edn, ed. Langer GA, pp 325-393. Academic Press, San Diego.

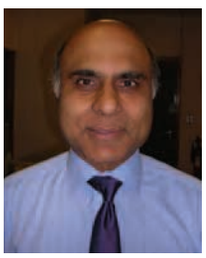
Huser J, Wang YG, Sheehan KA, Cifuentes F, Lipsius SL & Blatter LA (2000). Functional coupling between glycolysis and excitation-contraction coupling underlies alternans in cat heart cells. *J Physiol* **524,** 795-806.

Kockskamper J & Blatter LA (2002). Subcellular Ca^{2+} alternans represents a novel mechanism for the generation of arrhythmogenic Ca^{2+} waves in cat atrial myocytes. *J Physiol* **545,** 65-79.

Kockskamper J, Zima AV & Blatter LA (2005). Modulation of sarcoplasmic reticulum Ca^{2+} release by glycolysis in cat atrial myocytes. *J Physiol* **564,** 697-714.

Ventura-Clapier R, Garnier A & Veksler V (2004). Energy metabolism in heart failure. *J Physiol* **555,** 1-13.

Hepcidin, body iron and infection



Ted Debnam (left) and Kaila Srai

Iron deficiency anaemia is the most common nutritional disorder affecting over 30% of the world's population. In developing countries the condition is frequently exacerbated by infection. There is no excretory pathway for iron and body iron status therefore depends on the efficacy of dietary iron uptake. This process is suppressed by hepcidin, a liver-derived peptide that is also an antimicrobial agent.

Adequate levels of iron are central to tissue function but the metal is toxic in excess. A healthy 70 kg adult contains 3-4 g iron, most being a constituent of haemoglobin or myoglobin. Each day round 20 mg of body iron is recycled through reticuloendothelial macrophages in spleen, liver and bone marrow, this being a consequence of normal erythrocyte turnover.

By comparison, the daily obligatory body loss of iron (via urine, GI tract and skin) is small, some 1-2 mg. Nonetheless, if this is not replaced by duodenal uptake of an equivalent amount of dietary iron, the inevitable long term consequence will be iron deficiency. Only about 10% of dietary iron needs to be absorbed by the small intestine to match obligatory losses, but the body has the capacity to increase this proportion in times of higher demand, e.g. pregnancy, or to meet the requirements for enhanced erythropoiesis during haemorrhage or hypoxia. Conversely, the response to increased body iron is reduced intestinal iron uptake. Although key elements in the mechanism for iron absorption across duodenal absorptive cells (enterocytes) are known, the way in which the overall process adapts to altered physiological demands is less clear.

The first link between inflammation and intestinal iron transport came from studies using the turpentine abscess technique to induce an inflammatory state. The procedure reduced duodenal iron transport in mice (Raja *et al*. 1990). A major thrust came with the identification of hepcidin in urine and plasma during a search for novel antimicrobial peptides (Ganz, 2003). Hepcidin, also called liver-expressed antimicrobial peptide 1 (LEAP-1), is synthesized by hepatocytes and is now known to be crucial for body iron homeostasis by acting as a negative regulator of iron exit from enterocytes and reticuloendothelial macrophages (Fig. 1). An injection of turpentine increases the expression of hepcidin by 6-fold, and lowers circulating iron level in wild type mice but not in animals unable to express hepcidin. The strength of the evidence linking this 25 amino-acid peptide to iron transport is now so great that it has acquired endocrine status. There is a reciprocal relationship between the rate of intestinal iron transport and expression of hepcidin. Thus conditions such as dietary iron deficiency, hypoxia and haemorrhage are associated with decreased hepcidin expression and this leads to adaptive increases in iron absorption. Conversely, hepcidin expression is increased by iron overload and less dietary iron crosses the duodenum. We recently showed that injection of synthetic hepcidin reduces duodenal iron absorption in normal and iron deficient mice (Laftah *et al*. 2004). Others observed that deletion of the hepcidin gene promotes iron transport. The finding that hepcidin reduces iron transfer across cultured intestinal epithelium provides compelling evidence for a direct action of the peptide on this tissue.

How does hepcidin achieve its action on enterocytes? There is growing evidence that the peptide promotes the internalization and degradation of Ferroportin (IREG1), the protein necessary for iron transfer to the blood (Fig. 1). At the brush border, hepcidin also reduces expression of divalent metal transporter 1 (DMT1), which mediates iron uptake from the gut lumen. However, it is unclear whether this response represents a direct action of hepcidin or is a consequence of changes in enterocyte iron level resulting from reduced Ferroportin-

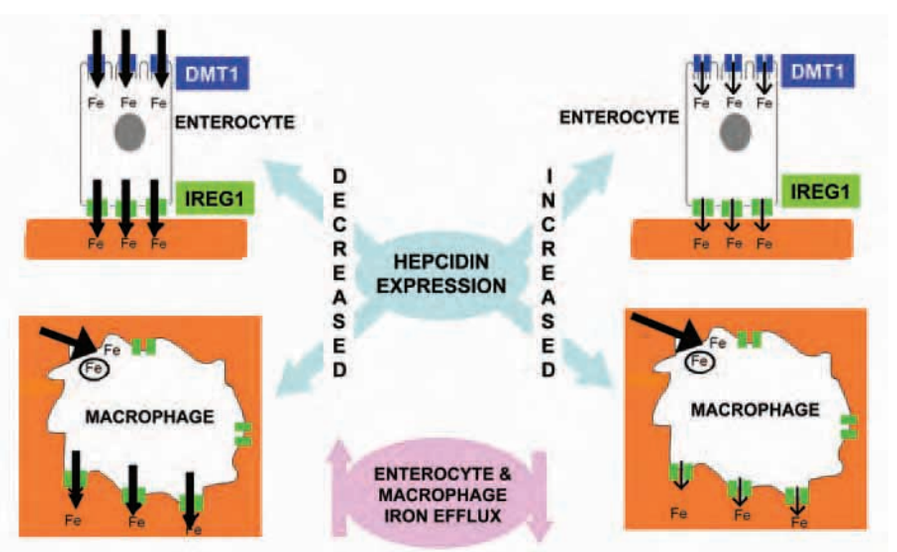


Figure 1. Hepcidin is a negative regulator of iron efflux from enterocytes and macrophages and acts by lowering the level of membrane Ferroportin (IREG1) in both cell types. The width of arrows indicates the relative rate of iron transport.

mediated iron efflux. The mucosal hepcidin receptor has yet to be characterized but some suggest that it may be Ferroportin itself.

The functional link between changes in body iron, hepcidin and duodenal iron uptake is unclear. Recent work suggests that altered hepcidin synthesis in response to an increased or decreased level of body iron involve the hepatic sensing of plasma transferrin iron saturation by a process involving TfR2 in concert with other proteins including TfR1, haemojuvelin and HFE (Frazer & Anderson, 2003). Our observation that hypoxia reduces hepcidin expression both *in vivo* and in isolated hepatocytes (Leung *et a*l. 2005) implies that hepcidin secretion is also linked to hepatic sensing of oxygen (Fig. 2). Inflammation is another recognized stimulus of hepcidin expression, an effect mediated by IL-6, but not TNF-α (Krause *et al*. 2000) indicating that hepcidin is a type II acute phase reactant.

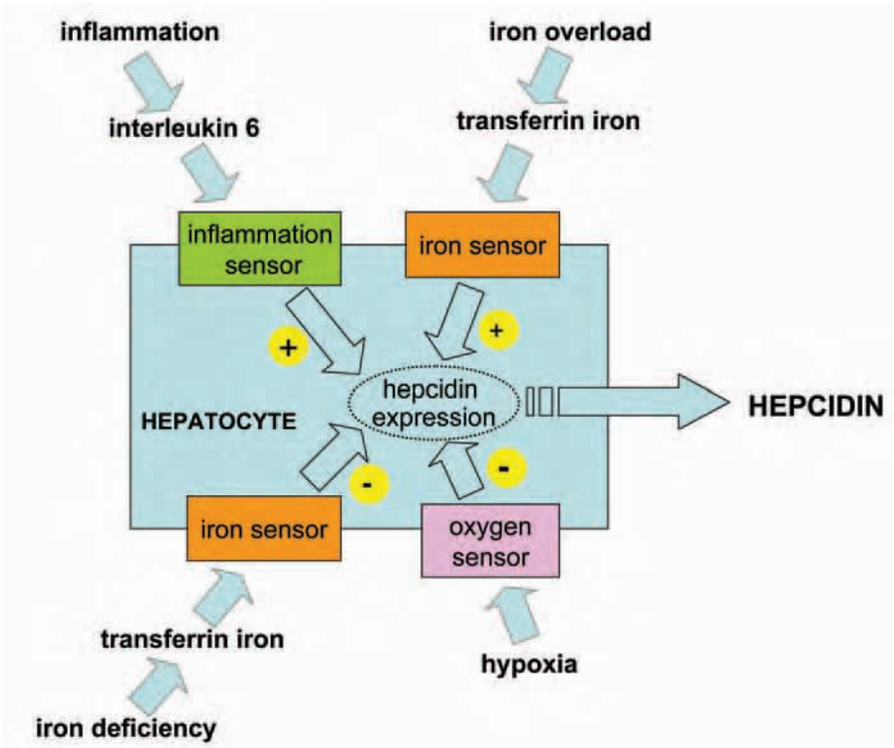


Figure 2. Hepatic sensors of inflammation, iron and oxygen serve to modify hepcidin expression. The specific 'sensing' pathways have not yet been elucidated.

The importance of iron and oxygen sensing linked to hepcidin expression and altered enterocyte iron transport is easy to appreciate. However, what is the survival advantage conferred by raised levels of hepcidin during inflammation? Interestingly, the peptide also reduces iron exit from macrophages by an action on Ferroportin, a process akin to that in enterocytes (Fig. 1). Macrophages can be regarded as reservoirs for iron, releasing the metal in times of increased body demand whilst storing iron to prevent circulating levels reaching toxic levels. The significance of the complementary effects of hepcidin on macrophages and enterocytes may be related to the requirement of iron for bacterial growth. By reducing iron efflux from macrophages and enterocytes, hepcidin will restrict iron availability to proliferating bacteria. Anaemia seems to be the price to pay for the fight against infection.

The anaemia of chronic renal failure (CRF) is usually attributed to inappropriate erythropoietin (Epo) secretion from a reduced kidney mass, but information suggests that hepcidin may also be involved. CRF patients receiving Epo often require iron supplementation to satisfy erythropoietic demands. However, oral iron tends to be less effective than systemic iron administration implying that intestinal transport of iron is inadequate. Interestingly, inflammation frequently accompanies CRF, particularly in patients on dialysis; not surprisingly, these patients tend to have raised hepcidin secretion. The peptide may therefore override Epo action in renal failure by acting on macrophages and enterocytes to reduce the availability of iron to developing red blood cells, culminating in iron deficiency anaemia.

A greater understanding of ways by which the liver influences iron handling by enterocytes and iron storage cells will throw light on the role of hepcidin in iron homeostasis in health and disease. Such knowledge may ultimately lead to tissue-specific therapies for more effective management of anaemia and other pathological changes in body iron.

Acknowledgements

Iron research in the authors' laboratories is currently funded by the BBSRC, the Roche Foundation for Anaemia Research and the National Kidney Research Fund.

Ted Debnam
Kaila Srai

Departments of Physiology and Biochemistry & Molecular Biology, University College London, UK

References

Frazer DM & Anderson GJ (2003). The orchestration of body iron intake: how and where do enterocytes receive their cues? *Blood Cells Mol Dis* **30**, 288-297.

Ganz T (2003). Hepcidin, a key regulator of iron metabolism and mediator of anemia of inflammation. *Blood* **102**, 783-788.

Krause A, Neitz S, Magert HJ, Schulz A, Forssmann WG, Schulz-Knappe P, Adermann K (2000). LEAP-1, a novel highly disulfide-bonded human peptide, exhibits antimicrobial activity. *FEBS Lett* **480**,147-150.

Laftah AH, Ramesh B, Simpson RJ, Solanky N, Bahram S, Schumann K, Debnam ES, Srai SKS (2004). Effect of hepcidin on intestinal iron absorption in mice. *Blood* **103**, 3940-3944.

Leung PS, Srai SK, Mascarenhas M, Churchill LJ, Debnam ES (2005). Increased duodenal iron uptake and transfer in a rat model of chronic hypoxia is accompanied by reduced hepcidin expression. *Gut* **54**, 1391-1395.

Raja KB, Duane P & Peters TJ (1990). Effects of turpentine-induced inflammation on the hypoxic stimulation of intestinal Fe3+ absorption in mice. *Int J Exp Pathol* **71**, 785-789.

The effects of spike activity on measures of neural encoding

Single neurones are driven to fire at precise times by certain features in their input. We have recently shown that the spike-triggering features reflect the influence of both the stimulus and previous spikes on firing probability

Individual neurones respond to particular features of their synaptic inputs and encode these features in their spiking activity. Although feature selection is generally assumed to arise from the patterns of connectivity in a neural circuit, neurones driven with a repeated complex current input fire precisely at certain times (Bryant & Segundo, 1976; Mainen & Sejnowski, 1995), showing that feature selection also occurs at the single neurone level. What feature or features of a time-varying current input cause a neurone to fire? How are these features determined by the neurone's biophysics?

The best estimate of the spike-triggering feature of the input to a neurone is found by applying a Gaussian white noise stimulus and using spike-triggered reverse correlation (de Boer & Kuyper, 1968) to compute the average stimulus trajectory preceding spikes (Bryant & Segundo 1976). This trajectory is known as the spike-triggered average, or STA. For many neurone types, STAs are characterized by a shallow hyperpolarizing trough followed by a more rapid depolarizing peak immediately preceding the spike (Aguera y Arcas *et al*. 2003; Powers *et al*. 2005). Examining this triggering process permits an understanding of the computation performed by the neurone. For example, the duration of the depolarizing peak in the STA may be a measure of the integration window for the detection of coincident synaptic inputs. Similarly, the hyperpolarizing trough in the STA may indicate that excitatory inputs are more likely to trigger spikes when excitation is preceded by inhibition.

Clockwise from top left: Randall Powers, Adrienne Fairhall and Marc Binder

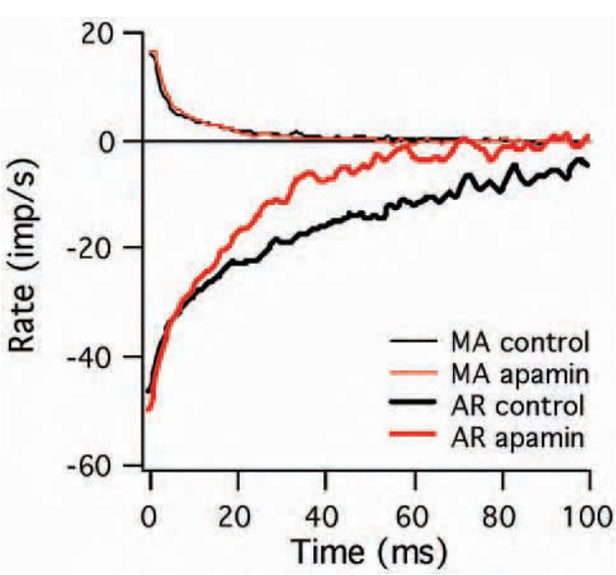


Figure 1. Selective reduction of the conductance underlying the mAHP reduces spike history effects on spiking probability. The spike history (AR) kernel is reduced (lower red vs. black traces) while the stimulus history (MA) kernel (upper traces) is unaffected by reducing the mAHP in a rat hypoglossal motoneurone with apamin.

The biophysical mechanisms governing feature selection in neurones can be difficult to disentangle. We and other investigators have proposed that the period of hyperpolarization in the STA may be required to decrease Na^+ channel inactivation for a short time, increasing the spike-triggering efficacy of any subsequent depolarizing input (Poliakov *et al.* 1997; Powers *et al*. 2005; Svirkis *et al.* 2004). Our recent work (Aguera y Arcas *et al*. 2003; Powers *et al.* 2005) shows that the shape of the STA also reflects the dependence of firing on the occurrence of previous spikes; in the case of motoneurones, through the medium-duration afterhyperpolarization (mAHP) mediated by SK-type Ca^{2+} -activated K^+ channels. We quantify this effect using an autoregressive-moving average (ARMA) process, which provides separate estimates of the contribution of spiking history (AR) and stimulus history (MA) to the spike probability (Powers *et al.* 2005). We find that the STA is composed of two components, one due only to the stimulus, and one reflecting the influence of the mAHP produced by the preceding spikes. Figure 1 shows the effects of the specific SK-channel blocker, apamin, on the MA (upper traces) and AR (lower traces) kernels before (black) and after (red) applying apamin to a rat hypoglossal motoneurone. Selective block of the SK-channels leads to a reduction of the influence of spike history on spike probability, as reflected by the smaller AR component, without affecting the influence of stimulus history.

Recently developed analytical methods (cf. Aguera y Arcas *et al*. 2003) allow us to extract a more complete picture of the features that trigger a spike. Computing not just the mean but the second order moment (specifically, the eigenvectors of the covariance matrix) of the spike-triggered stimulus distribution allows one to find a *set* of

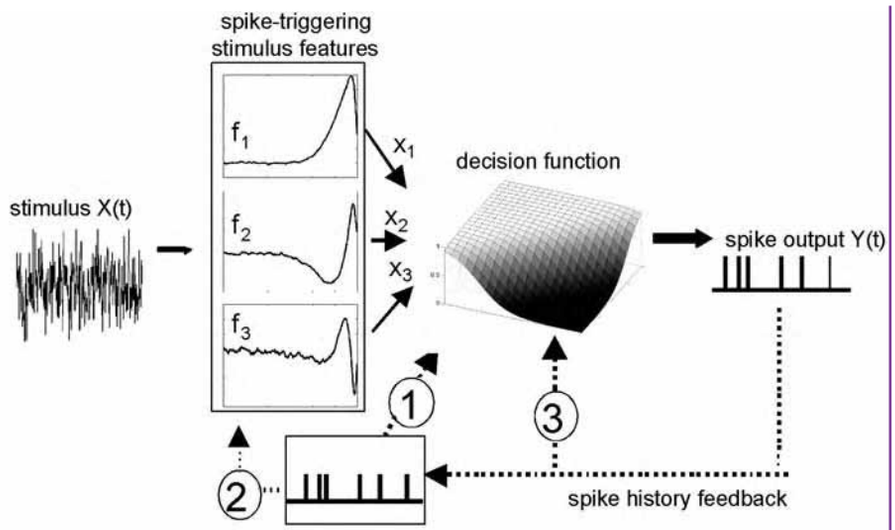


Fig. 2: Schematic representation of feature detection in neurones. Only certain features in the stimulus $X(t)$ are instrumental in triggering a spike. $X(t)$ is filtered through a set of linear filters representing the spike-triggering features to generate $\{x_1, x_2, .. x_n\}$. A multidimensional nonlinear decision function acts upon the outputs from these linear filters to give the probability of spiking. This generates the output spike train, $Y(t)$. However, the output spikes themselves act on the subsequent probability of spiking, either by (1) providing an additional input to the decision function (2) altering the shape of the spike-triggering stimulus features, or (3) by altering the nonlinear decision function.

stimulus features implicated in triggering a spike. The probability of spiking is then given by a decision function defined over that set of features (Fig. 2). The challenge is to determine how various aspects of this process are influenced by the biophysical features of different neurones. In particular, how does spike history determine the neurone's sensitivity to different features of its input? The figure posits three ways to represent the effects of spike history on the subsequent probability of spiking: (1) as an additional input to the decision function, (2) as an influence on the shape of the spike-triggering stimulus features, and (3) as an influence on the shape of the decision function.

Several labs (Powers *et al.* 2005; Aguera y Arcas *et al.* 2003; Truccolo *et al*. 2005; Paninski *et al.* 2004) are currently investigating a variety of methods to account for spike history in models of neural coding. These efforts are leading to a better understanding of how a neurone's own activity regulates its sensitivity to its inputs.

Acknowledgments

Work in our laboratories has been supported in part by grants from the National Science Foundation (IBN-9986167), the National Institutes of Health (NS-26840 and NS-31925), the Burroughs-Wellcome Trust and the Alfred P. Sloan Foundation.

Randall K Powers
Adrienne Fairhall
Marc D Binder

Department of Physiology & Biophysics, University of Washington School of Medicine, Seattle, WA 98195 USA

References

Aguera y Arcas B, Fairhall AL & Bialek W (2003). Computation in a single neuron: Hodgkin-Huxley revisited. *Neural Comput* **15**, 1715-1749.

Bryant HL & Segundo, JP (1976). Spike initiation by transmembrane current: a white-noise analysis. *J Physiol* **260**, 279-314.

Mainen ZF & Sejnowski TJ (1995). Reliability of spike timing in neocortical neurons. *Science* **268**, 1503-1506.

de Boer E & Kuyper, P (1968). Triggered correlation. *IEEE Trans Biomed Engr* **15**, 169-179.

Poliakov AV, Powers RK & Binder MD (1997). Functional identification of the input-output transforms of motoneurones in the cat and rat. *J Physiol* **504**, 401-424.

Powers RK, Dai, Y, Bell, BM, Percival, DB & Binder, MD (2005). Contributions of the input signal and prior activation history to the discharge behaviour of rat motoneurones. *J Physiol* **562**, 707-724.

Paninski L, Pillow, JW & Simoncelli, E. (2004) Maximum likelihood estimation of a stochastic integrate-and-fire neural encoding model. *Neural Comput* **16**, 2533-2561.

Svirkis G, Kotak V, Sanes D & Rinzel J (2004). Sodium along with low threshold potassium currents enhance coincidence detection of subthreshold noisy signals in MSO neurons. *J Neurophysiol* **91**, 2465-2473.

Truccolo W, Eden, UT, Fellows, MR, Donoghue, JP and Brown, EN (2005). A point process framework for relating neural spiking activity to spiking history, neural ensemble, and extrinsic covariate effects. *J Neurophysiol* **93**, 1074-1089.

Gilding the lily

I wanted to thank the magazine Editorial Board and encourage them to continue their refreshing look at the processes behind our scientific efforts with such editorials as discussions of 'gilding the lily' and our current predisposition towards hype (*Physiology News* **57**, 3)

Perhaps methodological soul-searching is one of the most important functions that our Society should perform. I was somewhat saddened to note that one of only two responses regarding gilding the lily was a comment on the source of the phrase rather than its relevance to our calling (*Physiology News* **58**, 45). Does this reflect a reluctance to question what we do and why? I hope not, because I feel that would be a fatal flaw in our ability to do what we need to do.

My personal view on gilding and hype is that they are very serious symptoms of the potential transmutation of science to alchemy. Gilding was perhaps an appropriate introduction! Why is this happening? Again, my personal view would be that it is our response to funding pressures. We need to be seen to be doing important stuff, so we have to make our stuff look important.

So are we going about this the right way?

Another personal opinion – no way! What makes science attractive enough to spend money on? What science does society spend their money on? How does that science make its appeal?

Take a recently-topical example: the origins of existence – quantum mechanics, string theory? (They even made a movie about it … what the *bleep* do we know?). What can physiology do to catch the imagination like that? It seems clear it's not about understanding (who understands quantum mechanics?), but about capturing the imagination. Giving people something they can be intrigued with. It is perhaps more the question than the answer … just a thought!

And what of the support of science … I don't know about the UK, but in the US the National Institutes of Health now provide a 10% funding level – down from around 70- 90% when I first started out in science ... years ago. The simple reality is therefore that an average scientist must write 10 grant proposals to get one grant. Ouch! Assuming a 1 month grant preparation phase (adjust as you please), that requires a 10 month investment for a grant which probably will provide funds for 3 years. Almost a 30% hit in productivity! Add the cost of reviewing 10 times the number of grants awarded, probably done by our more accomplished peers, and you have an immense amount of time spent chasing the funding rather than doing the science.

Now look to publications, the mere volume of which seems to indicate scientific prowess. What about information content, signal to noise ratio (as in repeating the same information in multiple papers)? Impact factors – do they confer a reliable measure of 'info content'/worth?

… Just a few thoughts!

John A Hodgson
UCLA, USA

Wobbles

Len Best's article about Wobbles (*Physiology News* **60**, 30) brought back memories of an incident on a hot summer's afternoon at Babraham in the 1960s. Catherine Hebb, who was keeping an eye on things during John Gaddum's absence, was summoned to his lab by a technician in trouble with some bioassays. Before lunch, the lever attached to her leech muscle preparation had been producing a classical smooth trace on a smoked drum in response to the application of various putatively acetylcholine-containing samples. Now the traces were erratic and saw-toothed. Catherine obtained the same bizarre results. Moreover, the lever continued to jiggle after the muscle bath had been emptied and the muscle washed with eserinised Ringer's solution. Clearly something in one of the test solutions had affected the muscle. It was soon established that the agent responsible was long-lasting and its effect resistant to atropine. What was it? Could it be identified in time to meet the next deadline for a Physiological Society Communication? Excitement mounted – until someone took a really close look at the set-up and noticed an army of Pharaoh's ants galumphing up and down the thread that attached the muscle to the lever.

Ann Silver
Honorary Member, Cambridge

Stem cell rush

Put them here..
Put them there..
Or stick them up..
Everywhere

If you haven't heard it, this is the chant of those who jumped onto the stem cell band wagon!

Many of them, clinicians who wish to improve their BQ (*Physiology News* **60**, 47), are trying to sell it as panacea for the beam in your eye or corn in the sole. Scientists turned technocrats and enterpreneurs are busy establishing cord blood and tissue banks! A senior physiologist confessed that the DG wanted him to insert them somewhere to obtain a big grant. A young clinician was stumped by invitations received to speak at three melas (euphemism for scientific conferences) organised by the government, even though she is yet to begin her experiments !

While stem cells are being infused into every corner and crevice of the body, I am yet to find convincing evidence of their therapeutic usefulness. Without basic laboratory work on the tissue environment and stem cell interaction, display of unusual scientific fervour and adventurism in the field of stem cell trasplantation, is unwarranted.

J Prakasa Rao
Department of Physiology
Christian Medical College
Vellore, India

British Neuroscience Association symposium

The Physiological Society-sponsored symposium *Does synaptic plasticity provide the substrate for learning and memory?* took place at the British Neuroscience Association's 18th National Meeting in April.

The speakers in this session considered the evidence for the long-held premise that in order for animals to be able to learn or remember, lasting changes in synaptic transmission (synaptic plasticity) must take place within the CNS.

Richard Morris (Edinburgh, UK) considered the criteria that should be fulfilled in order that the question of whether plasticity subserves memory could be fully answered. These include: detecting changes in synaptic transmission or detecting structural changes as a result of a learning experience in the brain of a behaving animal; that inhibition of synaptic plastic mechanisms should inhibit learning and memory; and, finally, the tantalising 'nobel prize winning' demonstration of mimickry – in this case artificially producing synaptic changes in the brain should produce a real detectable learning episode. A range of different experiments that have addressed the first 2 criteria were discussed. Unfortunately, the criteria of experimental mimickry remains, as yet, a distant dream.

David Bannerman (Oxford, UK) discussed the role of glutamate receptors in synaptic plasticity and learning and memory. He showed that knockouts of the GluRA AMPA receptor subunit had a deficit in LTP in the hippocampus. However, these same animals were unimpaired in reference memory learning tasks that rely on hippocampal function. The simple conclusion would be that hippocampal learning is not reliant on LTP. However, a working memory learning task dependent on hippocampus was impaired in GluRA knockouts. Therefore even within a single structure such as the hippocampus different types of learning must be subserved by different plastic processes.

Denise Manahan-Vaughan (Bochum, Germany) considered whether plastic processes in the hippocampus that produce long-term depression of transmission may be important for learning and memory. Until recently it was assumed that increases in transmission were likely to be the important storage mechanism for learning. However, the work discussed suggested that exploratory spatial learning was associated with decrements in transmission and, therefore, LTD type mechanisms may be important for processing and encoding spatial features to enable learning and memory.

Finally, Malcolm Brown (Bristol, UK) developed the argument that decreases in synaptic transmission of the sort that occur during LTD underlie the changes that occur during visual recognition memory. He presented data from parallel *in vitro* and *in vivo* experiments exploring mechanisms of LTD and recognition memory respectively. Utilising selective glutamate receptor antagonists he described experiments showing that the particular glutamate receptors involved specifically in LTD are also involved in recognition memory mechanisms.

Zafar Bashir
MRC Centre for Synaptic Plasticity, University of Bristol, UK

See also *Neuroscience by the sea*, a report of the main BNA National Meeting by Thelma Lovick (*Physiology News* **59**, 39)

Noticeboard

Notices for the Spring 2006 issue of *Physiology News* should reach the Publications Office by 6 January 2006. Please send contributions to lrimmer@physoc.org.

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

MOLECULAR TECHNIQUES FOR LIFE SCIENCES WORKSHOPS

PCR Theory and Practice
23-27 January 2006
A five day course to introduce participants to this core technique covering the basics to quantitative Real-time PCR. Cost: £740 (Standard); £629 (CPD Accredited)
For further information and application form visit our web site: www.caledonian.ac.uk/mtls or contact: Mrs J Pierotti, MTLS Administrator, Biological and Biomedical Sciences, Glasgow Caledonian University, Cowcaddens Road, Glasgow G4 0BA. Tel: 0141 331 3209; Fax: 0141 331 3208; Email: mtls@gcal.ac.uk

FEPS 2006

Munich, Germany
26-29 March 2006
Joint Scientific Meeting of the German Physiological Society and FEPS.
Contact Ulrich Pohl
Email: physio2006@med.uni-muenchen.de

The Physiological Society Meetings

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

University College London
5-7 July 2006
The Physiological Society Main Meeting and Annual General Meeting

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

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

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

For further meeting details please visit The Society's web site
http://www.physoc.org

Reflections of an ex-Chair

Stewart Sage looks back on three years with the Editorial Board of *The Journal of Physiology*

How many Cambridge Dons does it take to change a light bulb? Change? Similar sentiments about lack of change are often expressed about *The Journal of Physiology*, yet as I look back on my time as Chair of its Editorial Board (pictured below in Tenerife in 2003), change seems to have been a constant theme.

I opened my e-mail on the morning of 7 May 2002 to discover that I was the newly elected Chairman of the Editorial Board. I passed briefly through my lab on my way to the Society's Publication Office, suddenly conscious that I had a lot to learn and little time to do it. The Society, on the recommendation of the Editorial Board of *J Physiol*, had put the publishing contract for both of its journals out to tender and the tender deadline was drawing near. As I approached the office in a building emblazoned *Cambridge University Press* , it occurred to me that after 124 years that was a name that might soon no longer be associated with *The Journal*.

After a warm welcome from Ann Watson and her staff in the Distribution Office, the workings of which I understood fairly well from my time as a Distributing Editor, I was led into the Production Office by Carol Huxley and started trying to get my head around the much less familiar production side of the process. I left very aware of the unease of the staff whose futures were now far from certain and suddenly conscious of the enormity of what I had let myself in for.

Within a fortnight I was wading through a large box full of tendering documents and struggling up the steep learning curve presented by the journal publishing business. As the round of tendering meetings began, I was somewhat relieved that as the novice who had joined The Society's Publishing Tendering Group at the last minute, I had selected the same three publishers as everyone else for further investigation. The meetings and presentations from the selected publishers proved an interesting if time-consuming diversion from exam scripts and I was pleased by the eventual emergence of Blackwell as The Society's first choice as a new publisher for its journals.

The one down side of the proposed change of publisher was the implication for the staff. The Society was unusual in managing not only the manuscript distribution side of its journals but also the production side, taking care of copy editing and setting in house and sending camera ready copy to its publisher. As a consequence, it had acquired a skilled, dedicated and long-serving staff in Cambridge. Although it soon emerged from the negotiations with the new publisher that the distribution side of the process would remain with The Society, a decision to hand over production seemed likely. I did not need the question and answer session that I agreed to have with staff (against Society orders) to be aware of the sense of betrayal felt in the Cambridge office.

The loss of control over production was also not an idea that the Management Group or Editorial Board warmed to and the issue was one of the dominant themes of the first Board meeting that I chaired in early November 2002. Now renamed Chair rather than Chairman, I was sent to fight on behalf of the Board for the retention of copy editing in Society hands. After two meetings of the Society's Executive Committee this was secured. It was agreed that The Society would retain responsibility for copy editing although other aspects of production would pass to Blackwell. The retention of copy editing, and with it an important influence over production standards, was probably the most significant thing I achieved while Chairing the Board. The new publishing contract was finalised

shortly after this eleventh hour change and was signed in December 2002.

My first Board meeting had loomed large in my mind. I had missed the previous meeting that had given rise to the vacancy that I had filled, but I still recalled the five and a half hour-long meeting in November the year before, which saw Editors dashing to dinner with some business still unresolved. I wasn't sure that I would be any more successful at steering the Board's discussions than some of my predecessors, but unknown to others I had imposed a guillotine on my first meeting by not rearranging my 6 o'clock supervision that evening. In the event I had half an hour to spare before I had to teach. Fortunately this set the trend for the other Board meetings I was to chair (although the same cannot be said for all of the meetings of the Management Group).

That first meeting was concerned not only with the momentous business of the first change of publisher in 124 years, but also changed the governance structure of The Journal. The composition of the Management Group was redefined and some job titles were changed to make them more easily recognised by those outside of the Physiological Society. Chairman became the gender-free Chair, and Distributing Editors (DEs) became Senior Editors (SEs). This, however, opened up the problem of what to rename the post of Senior DE. To keep debate short the rather curious title of Designated Senior Editor was adopted. The post of Press Secretary disappeared altogether as it had become redundant with the creation of a full time Managing Editor position earlier in the year. All this came hot on the heels of The Society's own reforms, which amongst other things saw an attempt at proper budgeting and the establishment of cost centres. As a consequence, earlier that day the Management Group had been able to set a budget for *The Journal* in the coming year for the first time, rather than having to rely on piecemeal approaches, cap-in-hand, to The Society.

Probably the best perk of the Chair's job is deciding where the Board and

Perks of the Chair's job – choosing meeting venues, dinner menus and wines

Management Group meet (although choosing dinner menus, and more to the point the wines, comes a close second). I had no qualms about holding meetings in interesting places, as this was one way to reward Editors for the hundreds of hours of their time they gave up for nothing. I inherited a pattern of holding two Board meetings a year: a main, day-long meeting in the spring and a shorter afternoon meeting in the autumn. I chose to have my first main meeting as chair in Tenerife, to coincide with a Joint Scientific meeting of The Society and the Spanish Physiological Society. The second was held in Glasgow to coincide with a large scientific meeting of The Society and the third was held in San Diego at the time of the 2005 IUPS meeting, at which *The Journal* sponsored two symposia. The shorter Board meetings are normally held in Cambridge so that Editors can meet *The Journal* staff based there, although in 2004 the Board met at Blackwell's offices in Oxford to give Editors the opportunity to see our new publishers premises.

The Tenerife meeting in 2003 was notable for the excellent February weather, the protracted discussions about Impact Factors and the enthusiastic speeches of thanks from our Spanish guests at the Board dinner. It also saw an exciting presentation from Blackwell on innovations we could expect the following year, the decision to publish manuscripts online upon acceptance (rather than after copy editing), and unacceptably warm cava at the reception before an otherwise excellent dinner.

With the Impact Factor in mind, I carried out a survey of the citation fate of papers accepted in 2002 to present to the Board in 2003. This revealed that there was no major difference in early citation success between different sections of *The Journal*, but that one third of all papers remained uncited one year after publication. It also revealed that papers authored by Editors are cited more highly than the average. Unable to recommend that only papers from Editors be accepted, the Board instead adopted a recommendation first made in Tenerife, that the acceptance rate be reduced towards a target of 30% from its then level of 40%, in the hope of eliminating the weakest papers which were not receiving attention.

The Glasgow meeting in 2004 was held on 1 April and the date may have been in the minds of some of those contributing ideas during the brainstorming breakout groups. The more serious business centred on teething troubles with the new publishing process. Perhaps the most momentous decision in a historical context was the recommendation to The Society that abstracts from scientific meetings be no longer published in *The Journal*, although it was later decided to defer referring this to the membership until the issue of voting on acceptance of abstracts had been resolved. Editors enjoyed fine spring weather and excellent Scots' hospitality. Many Editors from overseas, unaware of how Glasgow has changed in recent years, were pleasantly surprised. However, one local Editor managed to appear with a black eye, perhaps the result of a Glasgow kiss, just to prove that not everything in Glasgow has changed. Similar problems did not arise when we met at Blackwell's new premises in Oxford the following September.

My last Board meeting was in San Diego in April 2005, just before the IUPS meeting. The venue was the W

Hotel, a modernistic place that managed to pipe music into the most surprising of places and had a heated beach on the roof. The Board debated changes to sectionalisation of *The Journal* at some length, inspired by concerns that some authors in high impact areas might not feel *The Journal* was a home for their work. There were also extensive discussions on open access and possible changes that might become necessary in the light of the announcements from the NIH and the Wellcome Trust on the matter. It was decided to recommend to The Society that submission and page charges be delayed as long as practicable. The Board did, however, agree to join Blackwell's open access trial, allowing authors the opportunity of paying for immediate open access for their paper. Strangely no one had availed themselves of this facility as of the time I left the Board.

My last formal duty on behalf of the Board was to co-chair one of *The Journal's* sponsored symposia at the IUPS. Although Bernd Nilus and I were concerned that our TRP symposium was scheduled on the last afternoon of the meeting, we needn't have worried. The session was well attended, the excellent speakers were well received and the symposium dinner was a nice end to a long and busy week in San Diego.

A few weeks later my time in the chair and on the Editorial Board was over. The 7 years I was on the Board has seen great change. When I joined the Board the debate was whether to publish online, now it is about how much longer we will publish on paper. When I started as a DE in 2001 the title pages and abstracts of manuscripts to be assigned arrived by fax and papers for review arrived through the mail, now we take for granted a fully electronic process from submission to proof. Seven years ago it could take a year from submission to publication, now it can take only weeks. And I could go on, but this manuscript is due yesterday…

Stewart O Sage
Department of Physiology, University of Cambridge, UK

New Editors for *The Journal of Physiology*

Trevor Shuttleworth (above) is Professor of Pharmacology and Physiology and in the Center for Oral Biology at the University of Rochester Medical Center. He obtained his undergraduate degree in zoology in 1968 at Queen Mary College, University of London. In his final year he was amongst a group of only five students who opted to take a special course in physiology that was run, and almost entirely taught, by Trevor Shaw. Under the supervision of Roy Freeman in the Department of Zoology at the University of Otago in New Zealand, his PhD concerned the mechanisms of ion transport by the gills of euryhaline teleosts. He worked as a postdoctoral research associate in the laboratory of WTW Potts, again studying mechanisms of branchial ion transport in teleosts, before joining the faculty of the University of Exeter as a lecturer in the Department of Biological Sciences and, in 1985, became Senior Lecturer and Reader in Animal Physiology. In 1988 he moved to the University of Rochester Medical Center in New York state, to take up a position of Associate Professor in the Department of Physiology which was chaired by Paul Horowitz.

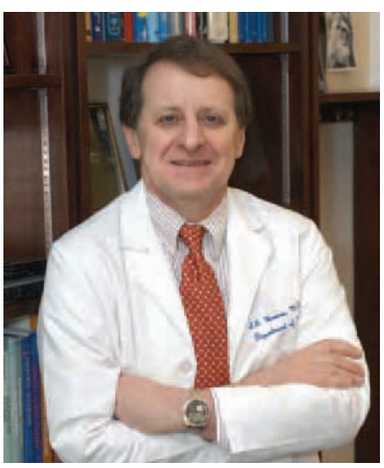
Although Trevor began his scientific life as a comparative physiologist, investigating mechanisms of epithelial ion and water transport in extra-renal salt-secreting organs, his work gradually became more concerned with the intracellular signals controlling these secretory processes. Since moving to the US, he has focused exclusively on cellular signaling pathways in non-excitable cells. Most recently, his studies have centred on the investigation of mechanisms of agonist-activated calcium entry in exocrine, and other nonexcitable, cells particularly noncapacitative (non-store operated) pathways of calcium entry. This has culminated in the discovery and biophysical characterization of an arachidonic acid-regulated calcium channel that appears to provide the predominant mode of agonist-activated calcium entry at low, physiologically relevant, levels of stimulation in many different cell types. Importantly, entry through this novel channel plays a critical role in modulating the frequency of the oscillatory calcium signals that are known to be responsible for the regulation of so many key cellular activities.

Kim Barrett (below) is Professor and Vice-Chair for Research in the Department of Medicine at the University of California, San Diego School of Medicine. Kim has focused her investigative efforts on the physiology and pathophysiology of the intestinal epithelium. Her work has defined key signal transduction mechanisms that regulate the process of epithelial chloride secretion, the main driving force for secretory diarrheal disease. She has also provided insights into the ways in which chloride secretion may be abnormally

regulated in the setting of intestinal inflammation and in response to enteric pathogens. Finally, recent studies have examined how probiotic microorganisms may exert protective effects on epithelial transport and barrier abnormalities evoked by pathogens or inflammatory cytokines. Kim received her PhD in bological chemistry from University College London in 1982, undertook post-doctoral training at the National Institutes of Health, from 1982-1985, and has more than 20 years of research experience in the area of epithelial biology that has received continuous funding from the US National Institutes of Health and other agencies, including the Crohn's and Colitis Foundation of America. She is also the recipient of awards from the Gastroenterology Research Group/American Gastroenterological Association, American Physiological Society and the Canadian Association for Gastroenterology and, in 2004, was awarded the degree of Doctor of Medical Sciences, *honoris causa*, from Queen's University Belfast, where she also held an appointment as a Visiting Professor from 1999-2002. She has played critical roles in professional societies, serving on

the Council of the American Physiological Society from 2001-2004 and on the Governing Board of the American Gastroenterological Association from 2004-2005. She has also been heavily involved in editorial activities, serving as Editor-in-Chief of the *American Journal of Physiology-Cell Physiology* from 1996-2002, and as a member of numerous international editorial boards. She also serves currently as Chair of the Publications Committee of the American Physiological Society.

Stephen Waxman MD, PhD (below) is the Bridget Marie Flaherty Professor of Neurology at Yale. He has served as Chairman of Neurology at Yale since 1986 and is the Director of the Neuroscience and Regeneration Research Center at the VA Medical Center in West Haven, CT.



Stephen is also Professor of Neurobiology and Pharmacology at Yale, and Visiting Professor at University College London. He received his BA from Harvard, and his MD and PhD degrees (1970, 1972) from Albert Einstein College of Medicine. Following Neurology Residency at Boston City Hospital/Harvard Medical School (1972-75), he held faculty appointments at Harvard Medical School and MIT, and then moved in 1978 to Stanford Medical School as Professor and Vice Chairman of Neurology, prior to moving to Yale in 1986. Stephen has published more than 500 scientific papers on molecular aspects of brain and spinal cord function, with an emphasis on ion channels and their roles in diseases of the nervous system. He has trained more than 150 neurologists and neuroscientists who work at institutions around the world. A member of the Institute of Medicine of the National Academy of Sciences, Stephen has served on numerous advisory boards and councils, including the Board of Scientific Counselors of the NINDS. His many awards include the Tuve Award from NIH, the Distinguished Alumnus Award from Albert Einstein College of Medicine, the Reingold Award from the National MS Society, and the Dystel Prize and the Wartenberg Award from the American Academy of Neurology.

Daniela Pietrobon (above) is Professor of Physiology at the University of Padova, Italy. After graduating there in Chemistry in 1979, she became CNR researcher in 1983, was visiting scientist at the Weizmann Institute of Science (Israel) for two years, and focused her research on energy transduction in mitochondria, for which she received the Luigi Galvani Prize of the Bioelectrochemical Society in 1985. Since 1987, when she spent 3 years in the Department of Cellular and Molecular Physiology at Harvard Medical School (USA), she has focused her research on the biophysics and neurobiology of voltage-gated Ca^{2+} channels. She became Associate Professor of the University of Padova in 1993 and Professor in 2000. In 2001 she was awarded the President of the Republic National Prize.

Experimental Physiology
Translation & Integration

Neural control of the circulation during exercise

In concert with *Experimental Physiology*'s commitment to focus on translation and integration, we will be publishing a series of articles on the theme of *Neural control of the circulation during exercise* in the January 2006 Themed Issue. These articles summarize recent information on the vertical integration of a myriad of neural signals emanating from active skeletal muscle and the brain.

Contributing authors include Paul Fadel, Kevin Gallagher, Mary Garry, Michael Joyner, Jere Mitchell, Donal O'Leary, Shigehiko Ogoh, Jeffrey Potts, Peter Raven, Scott Smith and John Williamson.

The use of exercise is the *sine qua non* in experimental investigations of integrated neural control mechanisms and clinical diagnostic testing of cardiovascular function. The invited articles in this thematic issue provide a review of current thinking regarding the roles of the two major concepts of neural control of the circulation during exercise, i.e. central command and the exercise pressor reflex, their actions and their interactions in influencing arterial baroreflex control of arterial blood pressure in health and disease. The articles cover a spectrum of investigative approaches using:

- clinical and integrative physiological measurements in animals and humans;
- studies identifying central neural mechanisms using electrophysiological and molecular biologic techniques in 'in vivo' rat and mice models;
- state of the art brain imaging techniques in humans.

A major unresolved question of circulatory control seeks the answer to whether the arterial baroreflexes are 'reset' to regulate the prevailing arterial blood pressure induced by the exercise or are they 'switched off" or 'ignored'? The bulk of the evidence indicates that the arterial baroreflex is 'reset'. Subsequently, the mechanisms underlying the 'resetting' at the organ system level in healthy human subjects and in how the baroreflex modifies the mechanisms of the exercise pressor reflex in the normal state and in the cardiac failure dog model are reviewed. The neurophysiological mechanisms involved are addressed using current

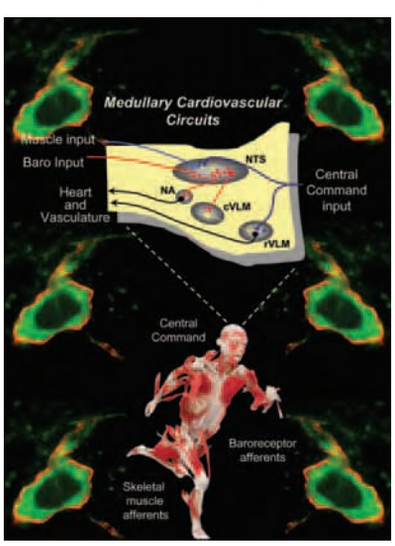
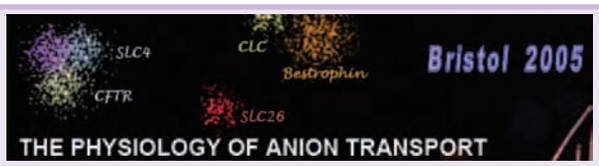


Figure from *Bodies: The Exhibition*, courtesy of Premier Exhibitions

molecular biological as well as state of the art imaging and complex monitoring of hemodynamic responses. In the past few years the scope of the investigations has broadened to address specific disease states such as, hypertension and congestive heart failure using cellular and molecular biologic techniques.

The invited and accepted original research submissions presented in this themed issue of Experimental Physiology provide a roadmap by which the clinician, the integrative physiologist and cellular and molecular biologist can address questions of physiology and pathophysiology concerning the neural control of the circulation during exercise. To develop these interactions, it is essential to establish a model of a working hypothesis which is based upon historical precedents to address the fundamental questions. Answering the questions raised by this model requires a multi-disciplinary experimental approach that marries molecular and cellular mechanisms with the physiological mechanisms of organ system function.

Peter B Raven
Department of Integrative Physiology, University of North Texas Health Science Center, Fort Worth, Texas, USA



The January 2006 issue of *Experimental Physiology* will include five symposium papers from the recent *Physiology of anion transport* meeting, which was held at the University of Bristol in July. This meeting was organised by David Sheppard (Bristol), Tzyh-Chang Hwang (Missouri, USA) and Mike Gray (Newcastle upon Tyne) and was a satellite conference of the Joint International Meeting of The Physiological Society and FEPS. It was the fourth in a series of biannual international anion transport meetings and was principally funded by The Physiological Society.

The aims of the conference were two-fold. First, to discuss the latest developments in anion transport, relating the molecular behaviour of anion channels and transporters to their physiological role in cells and tissues. Second, to highlight how a better understanding of anion channels and transporters is leading to the rational design of new therapeutics for a variety of human diseases.

These five meeting reports reflect the major themes of the *Physiology of anion transport* meeting. Paul Linsdell (Dalhousie, Canada) discusses the molecular mechanism of chloride permeation in the CFTR Cl^- channel. Anil Mehta (Dundee) explores the regulation of cell volume in epithelial cells, highlighting how the intracellular chloride concentration modulates the phosphorylation status of transport proteins. Makoto Suzuki (Tochigi, Japan) describes the molecular identification and function of a new class of Ca^{2+}-activated Cl^- channels ('tweety') that are widely distributed in excitable tissues. Michel Pusch (Genova, Italy) discusses the very recent finding that two members of the CLC family of proteins (ClC-4 and 5) function as Cl^-/H^+ antiporters and not Cl^- channels as originally anticipated. Michel's data have important implications for the physiological role of CLC proteins in intracellular organelles. Finally, Seth Alper (Harvard, USA) focuses on the molecular physiology of the SLC4 anion exchanger family. His report summarizes detailed structure-function analyses of SLC4 proteins, which have identified specific regions important for determining anion selectivity, regulation by pH and sensitivity to intracellular calcium. Overall the new data that has emerged provides a lucid understanding of how these transporters operate at the molecular level.

We very much hope that these meeting reports will give you a flavour of the stimulating discussions that everyone enjoyed during the 'Physiology of Anion Transport' meeting.

David Sheppard
Mike Gray

Wellcome (to OA publishing) Trust (us; it will be all right)!

The Wellcome Trust has notified grant holders that they must deposit papers based on funded research in PubMed Central and make them freely accessible within 6 months of publication. Regular contributors to the Society's journals have contacted us asking if they will still be able to send their papers to the journals because of the conditions in Blackwell Publishing's exclusive licence agreement which prohibit posting of the paper on public web sites within 12 months of publication.

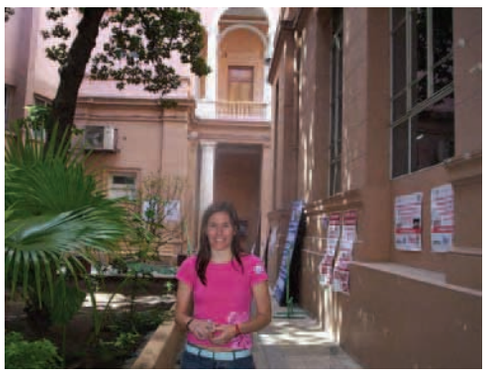
After some frantic behind-the-scenes activity, we can assure all potential contributors that they can still submit to the journals. The mechanism that will make this possible is Blackwell's Online Open option for open access (OA) publishing (http://www.blackwellpublishing.com/static/onlineopen.asp). Authors who are Wellcome Trust grant holders will be able to apply for funding to pay the Online Open fee of £1,250. Once the fee is paid the paper will be free immediately it is published and authors will be able to post the final version on PubMed Central at any time. Wellcome is prepared to pay the fee even if the research reported is only part funded by them and have awarded funds to their top 30 universities 'to cover the cost of OA publishing of any research paper resulting from Trust funding that has been accepted for publication in an OA journal or a journal that offers authors an OA choice for the payment of a fee'.

So all is well. Or is it? The Wellcome Trust funds around 15% of the research reported in our journals. How will their funding of open access affect subscriptions income? And will it equate to that income? Setting a realistic OA fee has been problematic for many publishers. What about invited review articles? Does this affect the independence of the peer review process? Questions to ponder as we move into the brave new world of OA publishing.

Carol Huxley

A postcard from Argentina

Laura Vanagas looks back on the first year of a Junior Fellowship in Cambridge



Back home in Argentina, Laura Vanagas (right) is now applying the methodologies developed in Cambridge to investigate whether glycosylation of the plasma membrane calcium pump may indeed be the mechanism responsible for the documented age-related decline in pump activity in these cells.

To give a taste of Argentina in a postcard, as David Eisner asked me to do, is not an easy task! Besides I am not a writer, and it is difficult to give a short and true description of this country given my own contradictory feelings about it. I love my country for many reasons (one of them being, of course, that I was born here). First of all, the variety and beauty of our landscapes are mind-boggling. Beginning in Patagonia, East and West are different worlds: the East has the amazing Atlantic coast where, at the right time of the year, you see the visiting whales; the West has the Andes, glaciers, petrified forests and lakes that will probably remind you of your English Lake district. As you travel North, in the centre of the country, you will see the Pampas, where everything is so plain and huge that you think it is boundless….or the low hills of Cordoba and San Luis, so similar in some aspects to the Peak district but on a vastly larger scale. Further on towards the North East, you find all the greens of Entre Rios (literally 'between rivers'), and lots of biodiversity in Corrientes, and Misiones with the jungle and the astonishing Iguazu Falls; and, finally, (because I could speak for ever about landscapes) the North West, with the magnificent mountains, the fine wines from Mendoza's 'bodegas', colonial cities, and the many remains from the Southern extensions of the Inca Empire.

Also I cannot forget about the people living in this country … because they are usually very kind and helpful, more so in the countryside than in the cities (where over 80% of the Argentine population lives). Perhaps you will be surprised when people kiss you on the cheek to say hello and good bye, and invite you to share some mate (a traditional infusion), but this is just part of our hospitality, and is one of the things I like most about my country. There is also a lot of solidarity, most of all from those who have the least, but who will share their meal with you even if they have nothing for tomorrow. I am not saying that this is a unique characteristic of our people, because when I had the opportunity to visit Cambridge for 3 months, thanks to a fellowship from The Physiological Society, I was received every where by people who generously opened their doors to me and gave me all they could to make my stay comfortable and make me feel at home.

But I have contradictory feelings about my homeland because, although I love it, there are lots of things there that make me sad. I think the main reason is the bad administrations we have had over the decades, and particularly the corruption in government. Of course, this is partly our fault, because in 22 years of democracy since the painful military dictatorship (itself the most terrible thing to happen in this country), we have been unable to choose good representatives to shape our destiny.

So when I write about Argentina's landscapes, I cannot forget that our governments do not take enough care of them, and that foreign investors are authorized to buy huge tracts of land for derisory sums. This has had dreadful consequences: lakes and large areas of outstanding natural beauty in the South have been privatized and we can no longer visit them. Mining by international corporations is being allowed without any restraints, resulting in contamination of the environment and leaving nothing but desolation for the local inhabitants ….these are just two examples.

Moving to science, despite decades of neglect and decay, Argentina still retains many centres of excellence in education and research. There are many excellent scientists, but research in biological or biochemical fields is a struggle. Even with sufficient funding, ordering chemicals and reagents is an ordeal; it may take a month or two to get them and the bureaucratic obstacles are a nightmare. Scientists are not well paid, and there is not enough money for research, so scientists here really have to feel science is a vocation, not just a career.

I find I am telling you of the many things that do not work in Argentina. Perhaps I have given the wrong impression – that I do not want to live in my country – which is absolutely untrue. I have tried to emphasise the good aspects too, because I want to live here, and see a day when things have changed for the better, allowing Argentina to become a country where all its people can live, study, and work.

Perhaps with help from more successful countries it will be possible at least to begin the process. The Physiological Society has allowed me to travel so far to pursue an interesting and challenging project on the mechanism of programmed red blood cell senescence. I have learned a lot in Dr Virgilio Lew´s laboratory, and back home I am now applying the methodologies developed in Cambridge to investigate whether glycosylation of the plasma membrane calcium pump may indeed be the mechanism responsible for the documented age-related decline in pump activity in these cells. I am most grateful to The Society for this marvellous opportunity and I hope they will continue with this kind of help to less developed countries like mine.

Laura Vanagas

News from the Annual General Meeting

The Society AGM was held at the Bristol meeting on 21 July. Following voting, Jonathan Ashmore, John Hanrahan, Christof Schwiening, David Sugden, Alex Tepikin and Teresa Tiffert were elected as new members of Council. Lord Turnberg of Cheadle, Bengt Saltin and Joseph Lamb were elected as Honorary Members. We are very pleased to welcome these colleagues. The new Council Members have already joined our various subcommittees and we look forward to involving them actively in the work of The Society. At the AGM several motions were discussed and it was agreed to reduce the number of Council Members to 20 over the next few years. Furthermore, as all Council Members will be Trustees of The Society, this ensures their direct involvement in The Society's strategic decision making.

The President of The Society, Alan North, gave a verbal report stating that this year had been one of exceptional change. This was the first year that a Meeting had included a public lecture, the first year without voting on approval of abstracts, the first year a meeting has been attended by a Minister – Lord Sainsbury of Turville, the Parliamentary Under-Secretary of State for Science and Innovation, and the first year *The Journal of Physiology* had been published by Blackwell Publishing after 125 years with Cambridge University Press.

Reports were also received from the Chairman of the Executive Committee, the Treasurer, the International Secretary, the Meetings Secretary and the Editorial Boards for *The Journal of Physiology, Experimental Physiology* and Biomedical Publications. The Articles of Association and Standing Orders were amended, with up-dated versions available for Members on request, and a motion that the production, copy-editing and approval of Proceedings Abstracts should in future be published in citable form on The Society's website, and not as a part of *The Journal of Physiology*, was agreed. Revised membership subscriptions were also agreed.

For your diaries, the dates of the following Scientific Meetings in 2006 and 2007 were approved. University College London, 5-7 July 2006 (The Society's Main Meeting), Ribeirao Preto, Brazil, 27-30 August 2006 (joint Meeting with the Brazilian Physiological Society), Glasgow, 8-12 July 2007 (joint Meeting with the Biochemical Society and the British Pharmacological Society), and Bratislava, Slovakia, 10-14 September 2007 (joint with the Slovakian Physiological Society and the Federation of European Physiological Societies).

Finally, it was agreed that the next AGM would be held during the University College London Meeting in July 2006, and we hope to see you all there.

Liz Bell

BIOSCIENCES FEDERATION

Building on success

This is the title of a major Biosciences Federation science policy report that will be launched at a symposium on 9 November. The speakers at the symposium – including Sir Richard Sykes (Vice Chancellor of Imperial College), Sir Keith O'Nions (Director General of the Research Councils) and Dr Ian Gibson MP (former Chair of the Commons Science and Technology Committee) – will be given an advance copy of the report and invited to address the issues raised in their talks.

The report deals with what has been the impact of government science funding policies on the health of the biosciences. It praises the benefits that have been achieved in infrastructure renewal; the balancing of the two arms of dual support offering the prospect of sustainability of research; the research strengths of most areas of bioscience being maintained or enhanced; the working relationship between universities and business being much improved; and both the government and scientists learning the importance of openness in engaging with the public.

But the report also draws attention to threats to the continuing success of the biosciences, some of which have been created or exacerbated by the government's tendency to central control and emphasis on accountability. This has introduced burdensome and unproductive bureaucracy and skewed priorities. Thus, conditions of employment of university researchers have been allowed to deteriorate, while the ring-fencing of money for centrally-driven initiatives has reduced responsive-mode funding. The flow-through of young people into bioscience has been influenced adversely by the importance attached to league tables of school examination results, which discourages pupils from choosing subjects perceived to be more difficult, and the impact of student debt discourages graduates from PhD study.

Full economic costing is sound in principle, but insufficient thought has gone into the recovery of overheads for charity, government department and European Union commissioned research, and the inability to cross-subsidise the cost of maintaining animal facilities may lead institutions to close them, to the detriment of training and research. There is a common opinion that the government has focused too much on university push rather than industry pull for knowledge transfer, which is leading to an over-emphasis on short-term research objectives.

Recommendations made as to how the government might modify its science funding policies to be even more successful in creating benefits for the public and the economy include cutting out unnecessary bureaucracy and allowing more university flexibility; putting in place a sensible academic career and salary structure; inviting the Funding Councils to determine without delay the real cost of providing a practically-based science course and supplying funding to enable the unit of resource to be increased; allocating funding for ring-fenced priorities from a new pool rather than raiding responsive-mode; and increasing the pool of 'third-stream' money so that universities can make strategic decisions on the types of research and knowledge transfer to pursue.

Copies of the report will be available during November, and there will be a pdf version at www.bsf.ac.uk.

Mike Withnall
Chief Executive, Biosciences Federation

Viva trauma

So let's talk PhD vivas. This is a topic which causes 3rd year PhD students to turn white, and can bring on post traumatic stress disorder-style flashbacks in veteran scientists.

A brief survey suggests that the most positive feelings most people can recall about their viva are 'relief', 'anti-climax' and 'thank heaven that's over'.

And those are the good ones. Everyone has heard the horror stories about the external examiner who wants to make the student re-write and re-submit the entire thesis 'because the wrong statistical test was used throughout'. Or the one about the student who arrives to find the external examiner is not the person s/he expected, but a far more eminent and forbidding interrogator. (If this last one sounds a bit far-fetched, I should say I have had at least one person swear that it really happened to them.)

Other phrases you do not want to hear from your examiners in the viva include:

'I was impressed by how carefully you had read my work … especially the long passage on page 36 that you copied from my 1995 review.'

[*Note to PhD students: while it is traditional (and probably advisable) to cite at least one of your external examiner's papers, you need to: (i) make sure the paper(s) appear in both the reference list AND the text (they always check); (ii) read them; and (iii) not copy them verbatim*.]

'I enjoyed reading your work on the effect of A on B. Of course, I might argue that all these effects actually occur because A changes C, and C then affects B… which I note you didn't consider at all…' (a long and meaningful pause usually follows here).

[*Note: Some highly skilled and experienced external examiners will then continue, after the pause: '... but I won't.' This is known in the trade as 'The Cambridge Gambit'*.]

At this time of the year, it is traditional to use these tales to scare the wits out of any over-running PhD students who are desperately trying to finish writing their thesis while on state benefits, or working 3 days a week in McDonalds or Starbucks.

As a result, students nearing the end of their PhD usually worry a great deal about the choice of examiners.

This is where the supervisor gets to make one of his or her key inputs. Three years of only seeing your supervisor monthly, or only in lab meetings, or finding they are always at a conference when you need them, can be redeemed at a stroke by the supervisor choosing the right examiners.

The internal examiner presents little problem. If s/he is not a friend of the supervisor, junior to them in the department or institute, or obliged to them professionally in some way, there is always good old-fashioned blackmail. And if the student has something on the internal examiner too (for instance involving drunken misbehaviour at the Christmas party, or even better afterwards in a nightclub, preferably captured for posterity on mobile phone camera or video clip), so much the better. It is difficult to really put the frighteners on someone if they have seen you doing a drunken Conga to 'Hi Ho Silver Lining', or falling over.

External examiners are more tricky. It is usually better to have an external PhD examiner in the middle years of his or her career, thus ensuring that s/he: (i) may be an old friend or colleague of the PhD supervisor; (ii) has done a good few PhD vivas and knows the form; and (iii) has a busy schedule and will thus only be able to spare a day. A further vital requirement is that the external examiner should have at least a 3 hour journey each way. This allows them to read the thesis on the way, and hopefully ensures their presence for a maximum of around 4 hours, which should consist of 2 hours lavish lunching (three small glasses of wine is considered optimum) and 2 hours (or even less) viva.

[*Note to PhD students: If the external examiner initiates the viva at 2.00 p.m. by announcing that s/he needs to catch the 4.00 p.m. train, you are usually home free.*]

At the other end of the spectrum, the Examiner From Hell typically come in one of two guises. The first is the fanatical first-timer, who insists on relentlessly applying the most exacting standards to every technique, figure and table in the misguided view that s/he is refereeing a paper for *The Journal of Physiology*. The second is the eminent authority who is convinced that standards have slipped disgracefully and 'wishes to take a stand'.

Needless to say, the careful supervisor tries to avoid either of these examiners. But some do slip through – hence the horror stories.

However, there is light at the end of the tunnel for nervous PhD students. Provided they have done the work, almost everybody makes it through – even with the Examiner from Hell on the job . A lucky few get to chat cosily to the examiners about that *Nature* paper derived from their first year work. Others spend 5 hours defending themselves against the Inquisition. Most people are, of course, somewhere in between. But at the end, everyone who passes gets a PhD.

The point here is that getting a PhD is more important than the precise manner of the getting. Some sail through their viva. Some get the 5 hour grilling and a re-write. But as long as the thesis is eventually accepted, they all get the reward for the 3 or more years of hard work learning to be a scientist. Not so much the title of Dr – occasionally useful for pleading with bank managers for overdraft extensions, although in the eyes of most people in the UK far less prestigious than the 'real' Dr conferred on medics – but the scientist's 'union card'.

For that is what a PhD is – not just recognition of the years worked, but recognition of proving you can pursue a scientific line of reasoning through hypothesis and experiment. And not just a title, but admission to a career in science, if you want it and are prepared to put the time in.

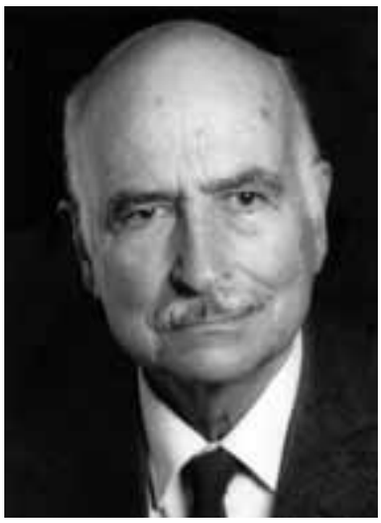
Just don't expect to get paid much.

And welcome to the business.

Mark Cain

Silvio Weidmann

1921 – 2005



Despite having an almost pathological fascination with languages, and being of a generation that needed as a student in the 1950s to read German in order to keep up with the scientific literature (what is now the *European Journal of Physiology*, was *Pflügers Archiv für die gesamte Physiologie des Menschen und der Tiere* and was published entirely in German), I confess that I never found it congenial. I put it all down to a very bad experience at school with a teacher of the German language. But there is nevertheless a book in German that I know almost by heart: Silvio Weidmann's classic *Elektrophysiologie der Herzmuskelfaser* (Weidmann, 1956).

To a student of cardiac electrophysiology starting work at UCL in 1958 this was the gold standard. During the late 40s and early 50s Silvio had swept the board with a phenomenal set of microelectrode experiments on cardiac Purkinje fibres, partly based on his first use of microelectrodes with Edouard Coraboeuf and Morrell Draper, during his highly productive period at Cambridge. He worked on Purkinje fibres of the heart while Hodgkin and Huxley were pioneering their voltage clamp and mathematical analysis of the squid giant axon. Of course, you can find Silvio's original papers in English mostly in *The Journal of Physiology* during the 1950s, but his book, just 100 pages long, brought it all together and is still a mine of insights, not all of which are to be found in the papers.

Having first missed the action potential overshoot in his 1949 experiments with Coraboeuf (Coraboeuf & Weidmann, 1949), he not only found it later, but also demonstrated its behaviour as an almost perfect sodium electrode. The resting potential was also shown to behave more approximately as a potassium electrode at higher levels of $[K^+]o$. Significantly, he also observed the membrane depolarization at very low $[K^+]o$, a result that was eventually explained by the action of external potassium in controlling the inward rectifier current, iK1, and which has had major implications for pathological states in cardiac tissue at low potassium.

But the most tantalising results were those obtained on membrane conductance. The paradigm for this investigation was Cole and Curtis's (1939) demonstration of the large increase in conductance during the squid nerve action potential, a result fully explained by the Hodgkin-Huxley equations (Hodgkin & Huxley, 1952). Silvio used repetitive square current pulses injected through one microelectrode while recording the potential changes with the other (Weidmann, 1951). He found the large increase in conductance during the action potential upstroke. But then surprises were in store. The conductance rapidly falls at the beginning of the long plateau and falls even below the resting level towards the end of the plateau. He observed a gradual fall in conductance during the pacemaker depolarization. It was also by using this method that he found the phenomenon of propagated all-or-nothing repolarization. This was a rich haul indeed from a single technique.

These repetitive pulse experiments were to prove critical for the subsequent analysis of ionic current mechanisms. The fact that the plateau conductance is very low presaged the discovery of the inward rectifier current, iK1, (Hutter & Noble, 1960; Carmeliet, 1961), since Silvio had correctly surmised that there must be a large fall in ionic conductance on depolarization. In retrospect, this was the easiest of the results to explain. The others posed problems that took many decades to unravel.

The slow decline in conductance during the pacemaker depolarization is consistent with a pacemaker mechanism dependent on decay in the delayed potassium current, i_{Kr}, one of the mechanisms found later to be important in sino-atrial node pacemaker activity. But, paradoxically, the Purkinje fibre pacemaker depolarization is generated by an increasing conductance to the hyperpolarizing activated current, i_f. How this could generate a fall in net membrane conductance during the depolarization itself had to await computer modelling for a full explanation. Confusingly, the fall in conductance is a consequence of the depolarization in this case, not its cause (DiFrancesco & Noble, 1985).

The fall in net conductance during the plateau also required mathematical analysis to unravel fully. In fact it took 30 years before Silvio's square pulse experiments were fully explained quantitatively.

Interestingly, Silvio himself did not participate in this mathematical unravelling of his seminal experiments. As he said himself in his 1993 autobiographical article in *Annual Reviews of Physiology*, 'I still belong to a group of individuals who have reasonably good intuition but are unable to describe results in terms of equations' (Weidmann, 1993). In fact Silvio's unease with mathematical analysis went even further. In the same article he blames my initial success with computer modelling (Noble, 1960) for preventing people thinking of additional ionic current mechanisms. Of course, this is partly correct. We should indeed beware of

being blinded by our hypotheses, even quantitative ones, however successful. But the other side of the coin is that finding gaps or errors in mathematical models has also been the engine of further experimental discovery (Noble, 2002). We should see modelling and experimentation as an iterative interaction. They don't replace each other.

Interaction with Silvio after the 1960 modelling work was very important to me personally, even though we never actually discussed any equations. I met him in 1962 at the first IUPS Congress that I attended in Leiden, where he chaired a symposium on cardiac electrophysiology at which I was asked to present my work reconstructing his conductance experiments. He told me that he had read my thesis on the beach in a single day and that it gave him a headache! No matter, he kindly presented me with a signed copy of *Elektrophysiologie der Herzmuskelfaser* which I treasure to the present day.

As a further aside on languages, another recollection that I have of the 1962 Congress was its multilingual nature. I recall papers given in 5 different languages (English, French, German, Italian and Russian). By 1977 (the Paris Congress) we were down to two, and after that we arrived at the completely monoglot situation we find today. The reasons are obvious and necessary, but let us recognise also that something important has been lost. To return to Silvio, the ease with which Swiss people switch naturally between four languages, and sometimes even five (Rumansch being the fifth) is admirable. The name 'Silvio' betrays an Italian influence, though there was no family connection with the Italian-speaking region. Nevertheless, Silvio lived up to his name and appropriately spoke Italian. He also spoke Swedish, learnt from his days in Torsten Teorell's laboratory in Uppsala. He was fluent in six languages.

Silvio's pioneering experimental work stands the critical test of time. The experiments are still the touchstone for many aspects of current work. As an example, he showed that lowering external sodium greatly reduces the action potential duration – a result that also tended to blind us to the existence of other ionic currents, such as calcium currents, since it was so easily explained by the 1960 model. Well, we are still unravelling this process, as the roles of sodium-calcium exchange and of late persistent sodium currents become clearer.

He was not only accurate and insightful as an experimenter, he was exquisitely careful about his own interpretations. His elegant writing, both in German and in English, in fact mirrors the man – a refined, carefully spoken Swiss gentleman who impressed everyone with his beautiful English, spoken with a musical Bernese accent. My favourite recollection of him is a presentation he made at the Physiological Society on his work on intercellular connections. He had shown that the space constant of a ventricular trabecular muscle was much larger than the dimensions of single cells (Weidmann, 1970). He presented his results and finished with a slide fitting them with cable equations, together with a wide Weidmann smile and the comment 'Alan Hodgkin gave me the equations'.

True to himself, Silvio never gave us any equations. But he gave us more than enough to think about in his beautiful and highly quantitative experiments. It is hard to think about the beginnings of cardiac electrophysiology without recalling his monument. He was the one who first took us inside the cell.

Denis Noble

References

Carmeliet EE (1961). Chloride ions and the membrane potential of Purkinje fibres. *J Physiol* **156**, 375-388.

Cole KS & Curtis HJ (1939). Electric impedance of the squid giant axon during activity. *J Gen Physiol* **22**, 649-670.

Coraboeuf E & Weidmann S (1949). Potentiels d'action du muscle cardiaque obtenus à l'aide de microélectrodes intracellulaires. Présence d'une inversion du potentiel. *Comptes Rendus de la Société de Biologie, Paris* **143**, 1360-1361.

DiFrancesco D & Noble D (1985). A model of cardiac electrical activity incorporating ionic pumps and concentration changes. *Philosophical Transactions of the Royal Society* **B 307**, 353-398.

Hodgkin AL & Huxley AF (1952). A quantitative description of membrane current and its application to conduction and excitation in nerve. *J Physiol* **117**, 500-544.

Hutter OF & Noble D (1960). Rectifying properties of heart muscle. *Nature* **188**, 495.

Noble D (1960). Cardiac action and pacemaker potentials based on the Hodgkin-Huxley equations. *Nature* **188**, 495-497.

Noble D (2002). Modelling the heart: insights, failures and progress. *BioEssays* **24**, 1155-1163.

Weidmann S (1951). Effect of current flow on the membrane potential of cardiac muscle. *J Physiol* **115**, 227-236.

Weidmann S (1956). *Elektrophysiologie der Herzmuskelfaser*. Huber, Bern.

Weidmann S (1970). Electrical constants of trabecular muscle from mammalian heart. *J Physiol* **210**, 1041-1054.

Weidmann S (1993). Cardiac action potentials, membrane currents, and some personal reminiscences. *Ann Rev Physiol* **55**, 1-14.

David McKie Kerslake

1923 – 2005

With the death of David Kerslake from cancer at his home in Yateley, Hampshire on 9 June 2005, human physiology, and thermal physiology in particular, has suffered the loss of one of its most academically influential leaders. Most of his fundamental research was carried out at the Royal Air Force Institute of Aviation Medicine (IAM) at Farnborough with applications to aviation, but his work and contributions at the Institute have provided much deeper basic physiological understanding of human thermoregulation.

Both of David's parents were school teachers and in the early years he attended a school established by his

mother in their own home. At 11 he won an open scholarship to Merchant Taylors' School at Sandy Lodge and, at 17, an open entrance scholarship together with an open Kitchener scholarship which enabled him to study medicine at St Mary's Hospital. After qualifying in 1946 he then completed his National Service as a Royal Air Force medical officer at RAF IAM. During the following 2 years he became a lecturer in physiology at St Mary's before returning to the Institute as a scientific officer, having now obtained a PhD (London) which was based on work he had done during his National Service. In 1950 he was appointed Officer in Charge of the Climatic Section at the Institute, the year he was elected a Member of The Physiological Society.

David played a major part in the specification for, and the design and construction of, the first class climatic research facility at IAM which came into operation in 1952. He also became associated with investigating the effects of hot and very humid conditions on navy personnel and the heat acclimatization of troops. Throughout his 20 years at the IAM David made major contributions to the understanding of how to reduce the effects of hot and cold stresses to which military aircrew are exposed. The work ranged from the specifications of the thermal environments in the cockpits of fast jet aircraft to the design and assessment of personal air and liquid conditioning garments. Beneath much of this applied research David continued to focus on the prediction of physiological states of humans exposed to hot environments. The subject demanded a blend of physics and physiological methodology, mathematics, and an advanced capacity to design experimental apparatus. This was his *nirvana* in which he accomplished so much. His ingenuity and skills as an experimenter are well illustrated by the sensitive continuously recording balance which he developed to measure the rate of sweat evaporation from nude subjects and which had an accuracy of ±0.1g at low and ±0.4g at high rates. The physics of local heat exchange coefficients was studied on cylindrical models and clothed dummies before a series of experiments was undertaken on human subjects. Many of the principles governing heat exchange at the skin surface were established, particularly the control of body conductance and the effects of local skin conditions such as skin temperature, blood supply, skin wettedness and hidromeiosis on the sweat response. The results of these experiments were published in a dozen papers over as many years exclusively in *The Journal of Physiology* during the 1950-60s.

1962 was a year when his achievements were recognised by the award of an OBE and a few months later a DSc from London University. In 1966 he was awarded the Vernon Prize of the National Institute of Industrial Psychology. On his promotion to Deputy Chief Scientific Officer at IAM it was recorded that 'the United Kingdom possesses in Dr Kerslake the outstanding scientist in the field of physiological effects of changes in the temperature of the human environment'. However, David did not wish to be promoted to more senior posts which would have moved him away from experimental science to management. He remained for a good many years as head of the Climatic Section, and grew concerned that he was blocking the promotion ladder for anyone else in his section. Eventually it was agreed that he should leave the section and, with one assistant, continue in a consultant capacity. It went well for some years until defence cuts demanded a reduction in staff in every section and changes in the direction of research at IAM. It was this that led to his early retirement in 1978.

One important pinnacle was reached in 1970 which will remain David Kerslake's lasting testimony. He completed writing a Monograph of The Physiological Society which was published in 1972 – *The stress of hot environments* – based on the theoretical and experimental work he had accomplished at IAM. The Monograph examined a problem close to the core of David's thinking – the construction of an index combining all environmental and related factors into a single figure indicating the degree of heat stress. Many other attempts, empirical and rational, have subsequently been made to refine this requirement, and most are based on David's step-by-step examination of the physical principles governing heat exchange at the skin surface. In selecting a heat stress index he emphasised the importance of the circumstances under which it was to be applied – 'the sharpest knife is not the best one for opening envelopes'.

David married Valerie Chenevix Trench in 1959 and they had two children, Caroline born in 1961 and Michael in 1962, who were brought up in their house at Yateley. After retiring, David established a new lifestyle and built his own small wind tunnel at home and used it for experiments. He and Valerie decided to become partly self-sufficient. They were presented with a goat kid and subsequently built up a small herd of goats which David milked morning and evening for 20 years, driving them each day to Yateley common making use of borrowed grazing rights. Up until his late 70s he continued to lecture in London University and at service institutes and to take part in academic life. David was a founder member of the UK Climatic Physiology Group established in 1966 which drew together leading human, animal and plant climatologists of the age, including Weiner, Edholm, Mount, Bligh, Blaxter, Monteith and Findlay. One of his memorable contributions at a recent meeting of the group concerned the theoretical analysis of thermal stresses experienced by trireme oarsmen.

His closest family have described his integrity, modesty, sense of humour and zest for intellectual inquiry. His friends and colleagues in physiology and at the IAM also clearly recognised these traits and, like his family, will remember his presence and miss him greatly.

Ken Collins
John Ernsting

Winter Book Special

A selection of the latest tomes to while away the winter evenings

From neuroscience to neurology

Neuroscience, molecular medicine, and the therapeutic transformation of neurology

By Stephen Waxman
2004, Elsevier. 544 pp, £77.50 (hardback)
ISBN: 0-12-738903-2

Stephen Waxman's book is conceptually excellent in that he endeavours, with much success, to show that neurology is now a therapeutic speciality offering effective treatments based in modern neuroscience.

The first part of the book is made up of 12 chapters and deals with development of a number of new therapies from inception to clinical introduction. In the second part, 17 diverse chapters deal with evolving therapies and technologies. Most of the authors are US or UK based, but the chapters are uneven in their coverage with no common structure. For example, not all chapters have summaries and many could make more use of tables.

Although the book contains a huge amount of useful information, with a good index, it could be better organised and clearly suffers from being an edited volume.

Unfortunately the production of the book is not up to the highest of modern standards, with some good quality colour prints relegated to the back, presumably to save on production costs. Many diagrams elsewhere would also have been enhanced by colour printing. No web links are given and there is no CD-ROM. This is a shame because, with more unity of style and better illustrations, this would have been a first-rate book. Perhaps these problems could be fixed for the next edition.

Bill Winlow

Brain and visual perception

The story of a 25-year collaboration

By David H Hubel & Torsten N Wiesel
2005, Oxford University Press. 729 pp, £29.95
ISBN 0-19-517618-9

In this beautifully presented book David Hubel and Torsten Wiesel present their key papers on vision, visual perception and the mechanisms by which the brain's visual mechanisms are acquired. The book is much more than just a catalogue of papers, starting with the biographies of the two Nobel Prize Winners and four chapters on the research background at the time. These chapters are in themselves fascinating and outline the pivotal role played in the development of their research by Steve Kuffler as well as other major figures in neurophysiology.

Each set of papers, many of which appeared in *The Journal of Physiology*, is preceded by a foreword describing the background to the work and how they went about it, using whatever equipment was available to them, particularly at the beginning of their collaboration. The papers also have an afterword describing their feelings about the publication and how it was received by other scientists at the time of publication. I particularly liked their comment on their 1960 paper on receptive fields of optic nerves of spider monkeys (*J Physiol* **154**, 572-580):

'*The first nine fibers we recorded in this entire project were all on center, and we began to wonder if we were onto a new discovery, that primate optic nerves were all on-centers, unlike those of cats. It was a great disappointment (or perhaps relief) when the tenth one turned out to be off-center*'.

Comments like this throughout the book illustrate the refreshing honesty of their approach and help us to understand what drove them to continue with each new set of questions. However, they make clear in the epilogue that explicit hypotheses were largely absent from their way of working and thinking and that they regarded their work mainly as exploratory. They also make the telling point that their grant proposals would now be criticized as not being 'hypothesis driven', which leads one to wonder if they would have succeeded in today's rather restrictive scientific environment. If you want a good critique of the retrospective codification of scientific hypotheses, then read page 705!

Zuckerman: Scientist extraordinary. By Bernard Donovan. Published by BioScientifica Ltd for the Society for Endocrinology and ZSL. 506 pp, £24.95 with **special reduced rate for Society Members of £18.50**. Order online from www.bioscientifica.com/products/books/bsbkoff.htm. A review follows in a future issue.

A special collection of Royal Society Premier Lectures, compiled and edited by Sir Brian Heap, comprises nine specially selected lectures from recent years, none of which have been published elsewhere. In addition, it offers a unique opportunity to read Francis Crick's last paper on consciousness, completed posthumously and published in this compilation. Subscribers to Philosophical Transactions of the Royal Society B: Biological Sciences can access the full content automatically online at www.journals.royalsoc.ac.uk. Non-subscribers can purchase the printed issue at the specially reduced price of £45 (usual price £115). To place an order please contact the Royal Society (details below), quoting reference TB 1458. To purchase individual papers, or for free abstracts, please visit www.journals.royalsoc.ac.uk.

Tel: +44 (0) 870 121 4224
email: royalsociety@twoten.press.net
post: The Royal Society, PO Box 20, Wetherby, West Yorkshire LS23 7EB, UK

All in all this is an excellent book and helps to set the work of Hubel and Wiesel in the context of real people doing real science. It also helps to connect the papers together in an appropriate set of sequences for those starting in the area – how it would have helped to have it around when I first started trying to teach visual physiology to medical students. The scientific papers are divided into sections on:

• Normal physiology and anatomy

• Deprivation and development

• Three reviews: their Ferrier lecture of 1977 and their Nobel Lectures from 1981, all of which are models of clarity.

If you are short of time, read the reviews first and then go back to the original papers.

Bill Winlow

Medical mysteries

The testament of a clinical scientist

By John Dickinson
2005, Book Guild Publishing. 518 pp. £15.95
ISBN 1 85776 976 7

Physiologists and clinicians often spend enjoyable time slagging each other off to their respective peer groups. Although both groups contain many people fully trained in the other subject, and although there is much ongoing and fruitful collaboration between the disciplines, there are still enough differences in everyday agendas, pressures and outlook to make such mutual dissatisfaction inevitable. Physiologists like to bemoan clinicians' superficial understanding of complex problems, while clinicians grumble about the irrelevance or unrealistic nature of physiological results when applied to clinical practice. Both complaints are true. Well, here is a book that should help to bridge the gap. John Dickinson, a clinician with a research interest in hypertension and a physiological turn of mind, has gathered together 42 'medical mysteries' which still present practical problems to clinicians and bafflement to physiologists interested in mechanism. They cover a wide range of topics, from multiple sclerosis and motor neurone disease, to coronary heart disease, finger clubbing, endometriosis, chronic fatigue syndrome and schizophrenia, to name a random sample. Dickinson considers the nature of each condition, adds clinical insights, presents what is known of physiological mechanism, points out what doesn't add up, suggests plausible answers (some more plausible than others) and poses unanswered questions. There is a wealth of stimulating, culture-bridging information here, for both physiologists and clinicians. The book deserves to be widely read: as a reminder that many clinically important questions remain without satisfactory explanations, as an aid to mutual understanding, and as a source for new ideas and collaborations.

John A Lee

Physiology for nursing practice

Edited by S E Montague, R Watson & R A Herbert
2005, Elsevier. 839 pp, £27.99
ISBN 0 7020 2676 X

In these days of fully commercialised textbook writing, there are lots of perfectly reasonable, well-structured, nicely illustrated, clearly set out books to choose between. This is one of them. It covers all the usual stuff, with explicit attempts throughout the text to relate the physiology to clinical situations. What had me doing a double take with this text was the question 'Why would a student nurse need a 2 kilogram, 839 page text of physiology?' There's more in here than most medical students assimilate. Nurses simply don't need more than a fraction of it. What they need is to be able to look after patients on the ward, know when something's not right and call medical staff promptly. What they don't need to do and shouldn't attempt to do, is to analyse the causes of a patient's circulatory shock, say, before calling the doctor. That's how unnecessary fatalities occur. This book represents a monument to the progressive academicisation of nursing practice which has happened over the last 20 years, causally coinciding with a disastrous decline in basic nursing standards on the wards, visible to any doctor, traditionally trained nurse, or person who has recent experience of ward care (either personally or through relatives). There's no doubt that this book will be welcomed and usefully used by a small elite of academically high-achieving nurses working in high dependency units and similar situations. But for me, it mainly highlights how much backtracking nursing has to do to reclaim its true professional ethos and direction.

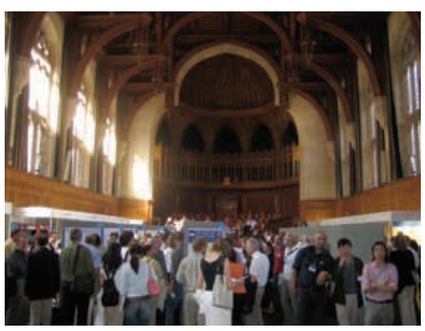
John A Lee

Neuroglycobiology

Edited by M Fukuda, U Rutishauser & R Schnaar
2005, Oxford University Press. 229 pp, £49.50
ISBN 0 19 852538 9

This is one of those books which is accurately described by its title. Eight chapters describe in detail recent research in the field. The opening chapter gives an overview of the structure, synthesis and function of neural glycoproteins and will interest you if you want a thorough primer of these important substances. Other chapters review particular functions or types of compound, including HNK-1 glycans, glycosphingolipids, gangliosides, roles in plasticity, insights from modification of biosynthetic pathways, effects of mutations affecting glycoprotein glycosylation, and the clinical lysosomal glycosphingolipid storage disorders. Having read this, you'll either be excitedly ready to order a copy, or you won't. There's no doubt that these substances are key players in neural development, structure and function to an extent that most of us are only dimly aware of. This book will be a helpful source for those currently active in the field, or those wanting to enter it. Apart from perhaps the first chapter, it is not aimed at a general readership.

John A Lee



Clockwise from top left:
Giovanni Mann (right) and Jonny Goodchild prepare a late lunch for Society staff at the Cambridge Publications Office BBQ in August.

Images of Oxford: The fair; The pavilion; St Giles; Nets (*more images of Oxford appear on the inside front cover and p. 5*).

Images of Bristol: Delegates catch a speech at The Society Dinner; Isambard Kingdom Brunel (not) tries his luck; Poster session in the Great Hall (*more images of Bristol appear on p 8*).

The Journal of Physiology Designated Senior Editor George Augustine in Cambridge on his engagement to Hideko Nomura.

(*photos by Austin Elliott, Prem Kumar and Emma Ward*)