PHYSIOLOGYNEWS

spring 2007 | number 66

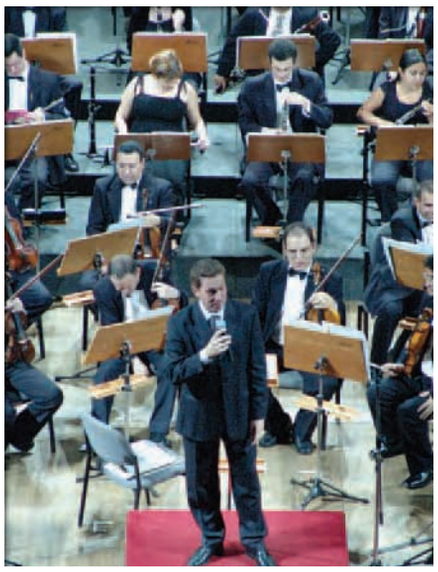
Meetings

Edinburgh
Belfast
Brazil

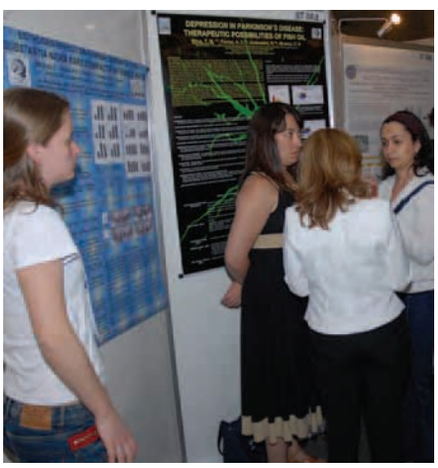
Also featuring

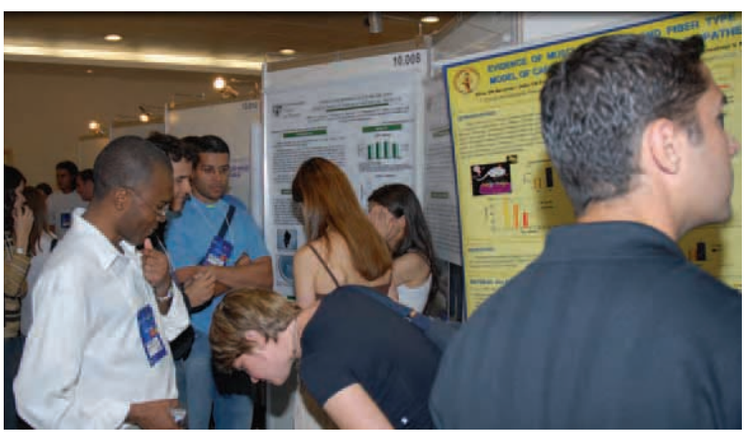
Peter Stanfield's 10 key papers ... and some music
A critical look at Lord Adrian's 1933 classic
Tim Bliss and LTP
Physiologists having fun on the road
The Journal of Physiology symposia
Warning: ethics can kill
Education – new feature

A publication of The Physiological Society



Joint International Meeting with the Brazilian Physiological Society Ribeirao Preto, Brazil 27-30 August 2006





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

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Contributions and Queries

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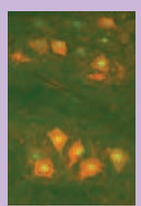

Image from *The Journal of Physiology* Symposium *The cortex, interneurones and motoneurones in the control of movement* to take place in Darwin on Thursday 19 July 2007. See page 40 for details



Images from *A week in the life of ...* (p. 13)

PHYSIOLOGYNEWS

Action points

Grants

For full information on Members' and Affiliates' Travel Grants, Network Interaction Grants, Non-Society Symposia Grants, Vacation Studentship Scheme, Departmental Seminar Scheme, Centres of Excellence and Junior Fellowships 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 7 days 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: imagre@physoc.org or updated online at http://www.physoc.org

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Physiology News

Deadlines

Letters and articles and all other contributions for inclusion in the Summer 2007 issue, No. 67, should reach the Publications Office (lrimmer@physoc.org) by 23 April 2007. 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 Board 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 Board of *Physiology News* tries to ensure that all articles are written in a journalistic style so that they will have an immediate interest value for a wide readership and will be readable and comprehensible to non-experts. In particular, scientific articles should give a good overview of a field rather than focus entirely on the authors' own research.

Format of articles

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

Length of articles

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

Submission of articles

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

Illustrations and authors' photographs

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

References

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

In this issue

Welcome to the first Physiology News of 2007.

The best bit of being an editor is to see new features inaugurated, and I am delighted to say this issue has two. The first is a regular column aimed at teachers in schools and colleges, kicked off by The Society's Education Officer Donna Brown. As with all new features, volunteers to write articles will be needed sooner or later (usually sooner), so contact Donna if you would like to be involved.

The second new feature is 'From the Archives', where John Widdicombe looks back at a classic paper, recalling when he first read it and comparing his reactions then and now. If you fancy writing about a paper that stands out in your memory, or if you have mused about writing a 'My 10 Key Papers' but felt 10 was 9 too many, now is your chance. Again, volunteers please!

This issue also has a 10 Key Papers, this time ion channel papers chosen by Peter Stanfield, and a Living History – not for the squeamish! – from John Dickinson. We also have seven scientific News and Views features, a Week in the Life of a physiologist on the road, plus meeting reports, Society news and book reviews.

Finally, I am a great fan of historical articles, and the longer I work in physiology, the more amazed I am by just how much the pioneers in various fields achieved with primitive and often self-built equipment. But historical articles also provide wonderful unexpected glimpses of people. For us normal bunglers it is good to know that even the scientific immortals couldn't do everything perfectly, so I treasure the revelation that Bernard Katz wasn't the greatest micropipette puller (see Liam Burke's memoir). Heroes should be human too.

Austin Elliott

Real science needs you

As 2007 dawns, a straw poll of the issues facing The Physiological Society and its Members might include, *inter alia*: the upcoming Research Assessment Exercise; the impact of full economic costing for grant applications to government–funded bodies, particularly the Research Councils; and the looming Tsunami (at least for learned societies that run journals) of open access and the potential loss of journal subscription income.

All of these issues are worth an editorial apiece, and I hope *Physiology News* will come back to them all during the year in one form or another. However, for this editorial I want to talk about one of my other recurring themes; the ever-growing tide of scientific 'disinformation', and how this potentially shapes the public's view of science, scientists, and scientific issues.

This topic needs highlighting, I think, because it is something of a Cinderella issue. What I mean by this is that it does not impact on us day-to-day in the same direct way as the others listed above do. For instance, I would guess that many Members have spent some time this last year cursing while they filled in a pre-RAE census form, trying to track down someone who can tell them how to fill in an FEC-costing sheet, worrying about whether The Society might have to charge a hundred pounds a go for meeting registration fees if full open access publishing comes in, or even pondering whether to publish something in an author-pays online open access journal.

In contrast, you probably haven't worried that much about any of the following: the Human Fertilization and Embryology Authority (HFEA) prohibiting scientists from making new experimental 'hybrid' stem cells by injecting human somatic cell nuclei into enucleated animal eggs (1); the new UK rules on labelling homeopathic 'medicines' discussed in our last issue's editorial; the opinion poll a year ago that suggested nearly half of Britons felt 'intelligent design' should be taught in science classes (2); the mass experiment in Durham feeding omega-3 fish oil supplements to all O-level pupils, which has no control group or blinding but has been widely described as a scientific trial (3); or the alarming prominence on British TV of self-styled 'nutritionists' and 'diet doctors' who find a lack of any formal scientific qualifications no bar to lecturing members of the public about what is supposedly going on in their bodies.

If you were a pessimist you could look at the issues just cited and say that science is, pretty much as a matter of routine, misquoted, misunderstood, and misappropriated. And that people on the receiving end of it – the public – are misinformed and misled.

The usual reaction from scientists is a weary shrug of the shoulders.

I would like to offer a counter-view. Rather than shrugging, we should be doing something. And I mean each of us.

First, though, one has to ask: why are we scientists so apathetic about junk science?

One can justify the prevailing apathy in a number of ways. The first is the view that the misreporting of science, and even more the full-on pseudoscience, is so crazy that no-one could possibly believe it. To which one might cite the poll on creationism, or the accounts from tropical medicine specialists indicating that some people travelling to malarial regions can, and do, believe that homeopathic preparations will offer malarial prophylaxis (4).

Another viewpoint is that it doesn't matter if lots of people believe utter nonsense, as long as the people who matter listen to the experts. To which one might cite the homeopathic medicine labelling debacle, where the interests of the homeopathic 'industry' clearly weighed heavier for the government than the scientific and medical opinion.

A third view is that we cannot do anything about what people believe. Well, we can. It is called explanation – or education. It may only have an effect on people whose current views are based on misunderstanding but, as we have seen, there is an awful lot of misunderstanding about.

The final viewpoint, which is where I suspect most of us end up, is that we deplore all this but feel there is nothing much we can do about it.

Which is where I beg to differ.

So what can we do?

It would be nice to think that the Royal Society, or the learned societies in concert, might set up a 'science nonsense rapid rebuttal unit', bashing out quick and scientifically authoritative press releases debunking the current idiocy *du jour*. Actually it would not be as hard as it sounds, since in most cases the original source – press release or published paper – of a ridiculous media science story is easy to find, and the errors in how it has been misreported are not that subtle.. However, unless there is something of a change of heart it seems unlikely that the UK scientific establishment will 'go public' in quite this way, so we will probably have to rely on bloggers like the excellent Ben Goldacre in *The Guardian* (3) or our own David Colquhoun (5), the occasional courageous editor like the *FASEB Journal*'s Gerald Weissmann (6), and the people at Sense About Science (4).

But there is something we can do ourselves – take some individual action, at the grass roots level, to promote real, evidence-based, science. Why not resolve, in 2007, to try one or more of the following:

• sign a petition against pseudo-science, or for the real thing. There are online petitions to sign, sometimes flagged up by The Society but also often via internet newsgroups devoted to debunking bad science, or promoting 'informed scepticism'.

• do something in your local school. This issue of *Physiology News* kicks off a new regular feature directed at school teachers. But initiatives directed at schools need people – you – to get involved to give them life. The universities are finally waking up to the need to get more involved with secondary school science, but how many Society Members, even those with secondary school age kids, actually offer to go and talk about working in science? Or about science stories in the news?

• email your MP. You can do this in minutes via sites like writetothem.com. For instance, the HFEA has defended its decision on hybrid stem cell cloning as 'sending the issue back to the politicians for more public consultation'. The final decision will come in the autumn. So now is your chance to tell your MP what you think. You may be quite sure those opposed to stem cell research will be making their voices heard.

• write to a newspaper. If you see a piece of scientific nonsense in a paper you read, don't just sit there – write and tell them exactly why it is wrong.

Because if you don't, no-one else will.

Austin Elliott

1 http://www.guardian.co.uk/science/story/0,,1989990,00.html
2 http://news.bbc.co.uk/2/hi/science/nature/4648598.stm
3 http://www.guardian.co.uk/life/badscience/story/0,,1873857,00.html
4 http://www.senseaboutscience.org.uk/index.php/site/project/73
5 http://www.ucl.ac.uk/Pharmacology/dc-bits/quack.html
6 Weissmann G. (2006) *The FASEB Journal* **20**,405-407.

Perinatal physiology: from uterus to brain

A Physiological Society Focused Meeting at the University of Edinburgh on 12 and 13 February

Invited speakers

Andrew Blanks (Warwick, UK)
Cathy Dwyer (Edinburgh, UK)
Abby Fowden (Cambridge, UK)
Dimitris Grammatopoulos (Warwick, UK)
Vivette Glover (London, UK)
Dave Grattan (Dunedin, New Zealand)
Mark Hanson (Southampton, UK)
Kelly Lambert (Richmond, USA)
Harry McArdle (Aberdeen, UK)
Simone Meddle (Edinburgh, UK)
Quentin Pittman (Calgary, Canada)
John Russell (Edinburgh, UK)
Julia Szekeres-Bartho (Pecs, Hungary)
Rachel Tribe (London, UK)
Joanne Weinberg (Vancouver, Canada)
Susan Wray (Liverpool, UK)

The meeting

The focus of this 2 day meeting, on 12 and 13 February, at the University of Edinburgh is perinatal physiology. We aim to draw together researchers from various active groups in the fields of neuroendocrine, placental and uterine physiology from within the UK and abroad.

Recent research in the field is highlighting important emerging issues such as the balance between brain and uterine/placental control of birth and perinatal behaviours, and the roles that neurohormones and immune signals play in regulating both elements.

The Centre for Integrative Physiology (CIP)

The meeting will be hosted by Alison Douglas and Mike Ludwig from the Laboratory of Neuroendocrinology in the Centre for Integrative Physiology (http://www.cip.ed.ac.uk), which was founded in 2005 as a focused research centre within the School of Biomedical Sciences. The scientific remit of the CIP is to investigate key physiological mechanisms from genes and cells to whole organisms. Investigators exploit appropriate model systems and focus activities that directly facilitate the understanding of human and mammalian physiology, development and disease.

Research in the Laboratory of Neuroendocrinology focuses on networks of neuroendocrine neurones that control all aspects of reproduction, as well as growth and metabolism, fluid and electrolyte balance, and physiological responses to stress, which are all of key importance to health and welfare.

The city

The University of Edinburgh is located within the centre of Edinburgh. Edinburgh was established as a UNESCO World Heritage City in 1995 and contains many visitor attractions, including Edinburgh Castle, Holyrood Palace and the Georgian New Town. Additionally, Edinburgh is known for its Festivals and hosts Scotland's 6 Nations International Rugby games at Murrayfield stadium. In fact, on the Saturday before the meeting (10 February) Scotland will be playing against Wales.

We look forward to welcoming you to The University of Edinburgh in February.

Alison J Douglas
Mike Ludwig
Centre for Integrative Physiology, School of Biomedical Sciences, University of Edinburgh

Above: Meeting organizers Alison Douglas (right) and Mike Ludwig. Far left: Sir Walter Scott monument. Left: Edinburgh seen from Holyrood Park.

For further information and online registration please visit
http://www.physoc.org/meetings/edin2007.asp

Above: Local organisersTim Curtis (left) and Graham McGeown. Right: Retinal arteriole showing smooth muscle cells and endothelial layers (provided by Norman Scholfield). Below: Queen's University Belfast (top) and the Students' Union

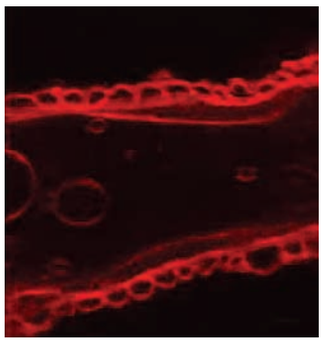
Ion channels and the microcirculation

A Physiological Society Focused Meeting at Queen's University Belfast on 4 and 5 April

Regard this as a personal invitation to Belfast in the spring-time! I know Belfast hasn't always been the most attractive of destinations; indeed, the Belfast of the 1970s featured as one of the 'hotspots' in PJ O'Rourke's book *Holidays in hell*. Thankfully, the 8 years since the signing of The Good Friday Agreement have been marked by ever-increasing political stability and remarkable economic growth. Belfast is booming, and in a good way this time!

This new growth and confidence has been paralleled with new academic appointments in the area of physiology, and five full-time staff have joined us within the last 2 years. For the first time in 20 years we have a truly international team of young researchers and teachers, mainly concentrated in the newly refurbished laboratories of the Cell and Metabolic Signalling Research Group.

It is a great privilege for us to host one of The Society's Focused Meetings



over Easter 2007. This will explore the role ion channels play in the microcirculation and follows the Annual Meeting of The British Microcirculation Society. The international speakers will describe recent findings based on techniques ranging from the molecular to *in vivo* physiology. The aim is to understand what makes the microcirculation, particularly resistance arteries and arterioles, so responsive to both the local needs of metabolically active tissue and the central requirements of cardiovascular homeostasis. Considerable emphasis will be placed on both K^+- and TRP channels but one sub-theme will be how changes in ion channel expression and control may contribute to vascular disease. Poster sessions will allow delegates to present their own results and several of the submitted abstracts will be selected for oral presentation, allowing younger researchers to discuss their work before a wider audience. Send in an abstract and it could be you!

There will be plenty of opportunity to meet people in a more informal setting as well, and there are good bars and restaurants all around the University area. The Meeting dinner is definitely not to be missed, as it will be held in Parliament Buildings at Stormont Castle, an imposing venue with plenty of history. Past experience suggests the food should be good too.

The last time The Society was in Belfast was September 1990, when 44 communications were presented. Let's see whether we can't double that score in April 2007.

Graham McGeown
Tim Curtis
Meeting Organisers

Peter Stanfield selects his top 10 ion channel papers ... and a piece of music

You know you are getting old when Linda Rimmer asks if you would contribute your top 10 papers to *Physiology News*. The task is easily accepted, but choosing only 10 papers among so many is more difficult, and I am sure if I had done this next week some, at least, of my choices would have been different. Since the 1960s, when I did my PhD, the ion channel field has changed markedly. Then, the concept of ion channels as membrane proteins was only in its infancy. And the great diversity of channels that we now know, first from electrophysiology but now more fully from molecular biology, was a strange, even heretical notion. The past 40 years have also seen a change in thinking from the domination in the early days by ideas from electrical engineering to an approach more familiar to biochemists. Nonetheless the seeds of current thinking were laid some time ago and a handful of papers generated hypotheses that have survived the examination even of structural biology.

Ion channels seem special in that they have a high turnover rate. We know from single channel recording that they carry current in the order of 1pA, equivalent to 6×10^6 monovalent ions in 1s. Chris Abrams, a former, gifted PhD student of mine, wrote in his thesis (Abrams, 2000) comparing an ion channel to the ticket barrier of a London underground station. The barrier bears about the same relation in size to the people going to catch their train as a channel does to the permeating ions. The barrier acts as a selectivity filter, permitting only those in possession of a ticket to pass through. Their luggage compares with the hydration shell of an ion and is temporarily given up during passage through the barrier. The jostling that occurs during rush hour is similar to the electrostatic repulsion that helps ions permeate. One difference is that the barrier opens and shuts each time a passenger goes through. A second is that if passage occurred at the same rate as it does in channels, the entire population of Greater London could go through a single barrier in little more than 1s.

Now although the speed of transfer can seem astonishing it is actually comparable to the turnover rates of the fastest enzymes, catalase and carbonic anhydrase. And I often wonder whether, if ionic transfer by channels had been discovered by biochemists rather than by those who are more attracted to the concepts of physics, they would simply have classed them as enzymes, catalysing the downhill movement of ions through the lipid bilayer. We would not then be asking students to write essays distinguishing ion channels from other transport proteins. Indeed, natural selection has not drawn the distinction, making a family of transporting proteins – the CLC family – that includes proteins we might classify as channels and those we might think of as transporters (Jentsch, 2006).

Peter Stanfield

Some, at least, of the papers I have chosen seem to me to be those that sowed the seeds of current understanding. But as well as being influential, they are attractive in the way the experiments are done and in the way they are written. Sometimes I can remember first reading the papers; often I have had the privilege of knowing the authors at least slightly.

1 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

Alison Brading also started with this paper (Brading, 2006). It is beautifully written, of course, but it is a more difficult read now because the convention used to ascribe a sign for current and voltage is no longer used. This is not an experimental paper, but is a mathematical description of currents recorded under voltage clamp and shown in other members of the series of papers that won the Nobel Prize for Physiology or Medicine in 1963. The description is so powerful that it dominated thinking for a very long time, and indeed still does. I am sure I am not alone in using *m, h*, and *n* as shorthand and in finding that the formulations (n^4 for example) resonate in the channel structures now known. In IT terms, these were early days to have computed the propagating action potential from the descriptions of current. But the paper also contained a most interesting insight, distinguishing the unitary event from the transfer of ions. Rejecting the hypothesis that sodium ions cross in simple combination with a charged carrier, because the carriers would carry initial outward current as they moved to the point where they picked up Na^+, the authors wrote:

> '*Changes in ionic permeability depend on the movement of some component of the membrane which behaves as though it had a large charge or dipole moment. It is necessary to suppose that (the) density (of these components) is relatively low and that a number of sodium ions cross the membrane at a single active patch*.'

Use of the word 'patch' seems prescient too.

2 Hodgkin AL & Keynes RD (1955). The potassium permeability of a giant nerve fibre. *J Physiol* 128, 61-88

The jostling of passengers on the underground is more annoying than helpful. But repulsion between ions is needed for fast permeation. This paper is the first description of single filing of ions through 'active patches' and almost certainly the first to propose that 'K^+ ions cross the membrane through narrow tubes or channels' whose diameter was 'little bigger than the hydrated potassium ion'. Here unidirectional fluxes were measured in metabolically poisoned axons, but a mechanical model (Fig. 1) was also constructed to help illustrate what was going on. In the axon, the ratio of unidirectional fluxes is very different from what is expected from the independence principle, where the movement of one ion is quite unaffected by the presence of other ions. The unidirectional flux from high

to low concentration is much greater than is expected, compared with the unidirectional flux in the opposite direction. Further, the flux ratio changes much more steeply with voltage than expected from independence. If the pore contains n ions on average, the mathematical description is:

$$\frac{j_o}{j_i} = \exp\left\{\frac{n(E-E_K)zF}{RT}\right\}$$

where j_o/j_i is the flux ratio, z is valency, E is membrane potential, E_K is the potassium equilibrium potential, and R, T, and F have their usual meanings. n turned out to be about 2.5.

3 Armstrong CM (1969). Inactivation of the potassium conductance and related phenomena caused by quaternary ammonium ion injected in squid axons. *J Gen Physiol* 54, 553-575

The quaternary ammonium ion tetraethylammonium, which is similar in size to a hydrated potassium ion, blocks potassium channels in squid axon only from inside. This paper from Clay Armstrong shows blockage by TEA^+ and other quaternary ammonium ions to depend on channels being open. Depolarisation produces potassium currents that are initially normal in appearance, but then inactivate as TEA^+ moves into the channel to block. The inner, cytoplasmic end of the pore is, then, wider and less selective than the outer part and access to this inner part of the pore is controlled by a gate, situated at its cytoplasmic end. The conclusion that 'a channel is either fully open or fully closed' echoes the notion of Hodgkin & Huxley that the unitary event is the formation of an active patch. In this paper also there is a dissection of the channel into parts that confer selectivity and parts that gate between open and shut states. The paper is the first of a brilliant series of great influence on thinking, particularly about how drugs act on ion channels. For example, the hERG channel in heart binds drugs rather promiscuously, causing acquired long QT and potentially causing death through ventricular fibrillation. Drugs bind in the wide inner vestibule of the channel and are potentially trapped there when

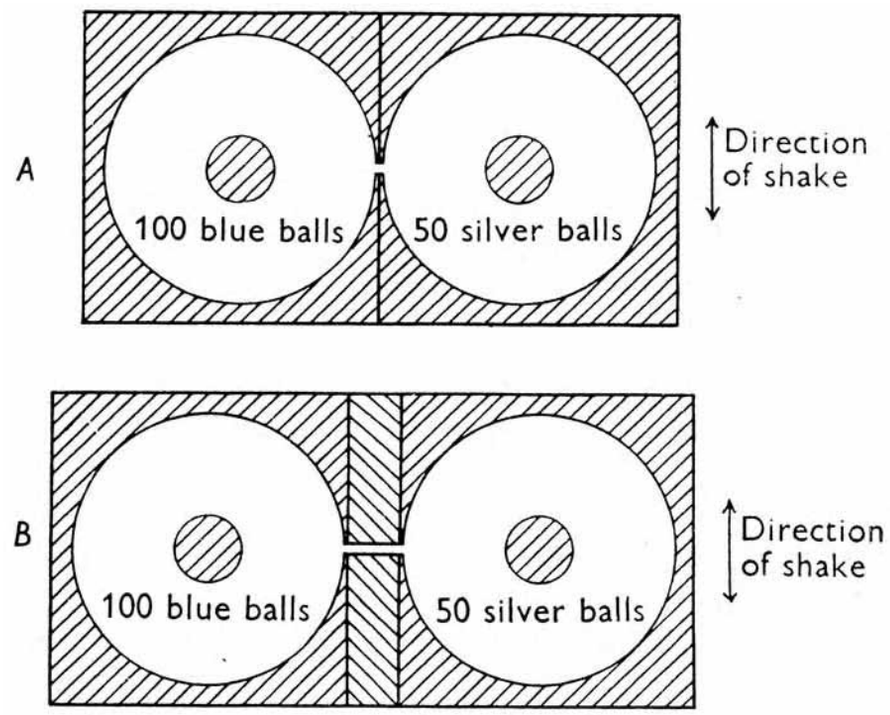


Figure 1. The mechanical model used by Hodgkin & Keynes to illustrate single filing of ions through a potassium channel. Small (3mm), coloured ball bearings were introduced into the two chambers as indicated, which were then shaken using a motor. Model A comes close to mimicking the independence principle, with flux from left to right 2.7 fold greater than from right to left (compared with the 2 fold difference expected). In Model B, a spacer is introduced so that the channel through which balls move contains several at any one time. Now the flux is 18 times greater from left to right. Reproduced from Hodgkin & Keynes (1955).

gates close (Kamiya *et al*. 2006), just as quaternary ammonium ions can be trapped by gates shutting. In this paper, Armstrong also made the proposal for potassium conductance of muscle – that 'metabolism of one class of TEA^+-like compounds' by muscle was responsible for the gating of what are now known to be channels of the inward rectifier (Kir) family and for the inactivation under depolarisation of the voltage gated potassium channels.

4 Hille B (1971). The permeability of the sodium channel to organic cations in myelinated nerve. *J Gen Physiol* 58, 599-619

This paper is not Hille's first paper on selectivity, but is the first on selectivity of a voltage gated ion channel. The selectivity filter of an ion channel is here seen at its simplest as working rather like the slot of a post (mail) box, permitting molecules of the right size to get through. But size alone is not enough and the permeating molecule interacts with the lining of the slot. In particular, molecules can be larger if they can hydrogen bond to the pore. Thus hydroxylamine permeates, but methylamine does not. The dimensions of the slot can be set at something like 3 × 5Å. A later paper in the series (Hille, 1973) looked at selectivity of potassium channels, suggesting a pore of 3 – 3.5Å diameter envisaging K^+ ions giving up their hydration shell to permeate. So Hodgkin & Keynes (above) were wrong only in thinking K^+ ions would retain their hydration shell.

5 Armstrong CM & Bezanilla F (1973). Currents related to movement of the gating particles of the sodium channels. *Nature* 242, 459-461

Hodgkin & Huxley had predicted gating currents and the fact that they could not measure them told them that the unitary event must be the creation of an 'active patch' through which many ions would pass. This paper was one of the first to measure these currents, which was also done at much the same time by Keynes & Rojas (1974). At about the same time also, Chandler & Schneider (1973) were measuring charge movements associated with the activation of excitation-contraction coupling in

skeletal muscle. The discovery of gating currents was aided by the ability to work on line to a computer, which could be used to subtract residual leakage currents digitally as well as the linear capacity currents (owing to charging of the lipid bilayer). This left the current associated with movement of the 'gating particles'. In terms of its timing, this current precedes the ionic current it permits (Fig. 2). Gating current is not blocked by the sodium channel poison tetrodotoxin, consistent with the separation of selectivity filter and gating; has an appropriate dependence on voltage; and has appropriate amplitude, with about 300 charges moving in each μm^2 of squid axon membrane, giving some 50 channels in this area. Later work established that the charge was immobilised with long depolarisations – *i.e.* the charge movement causing activation was itself inactivated by depolarisation. Thus activation and inactivation of sodium current were not completely separate gating phenomena as Hodgkin & Huxley had proposed, occurring independently in parallel with each other. Instead there was a linkage between the two.

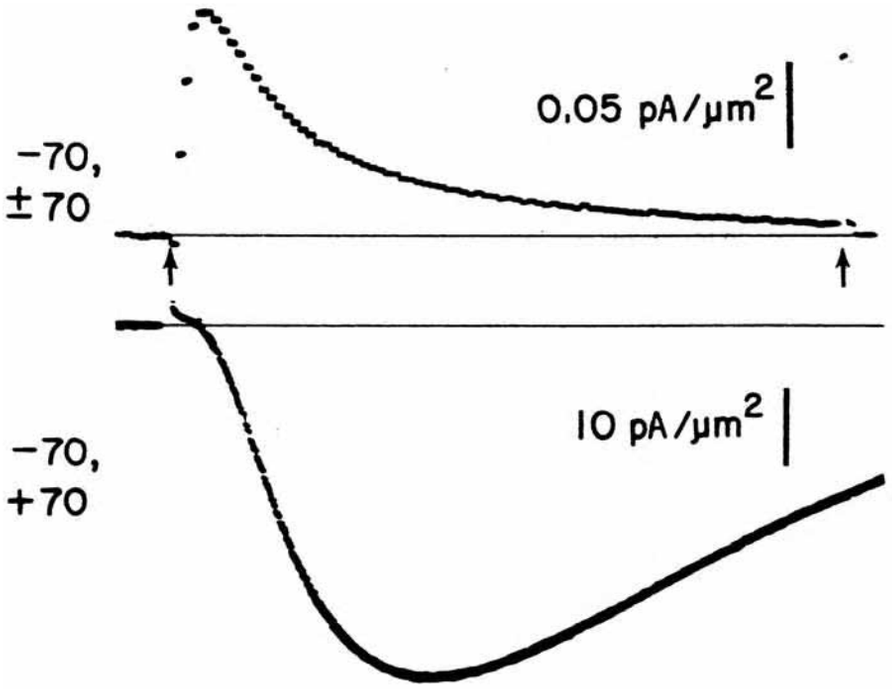


Figure 2. Gating current (above), measured in a squid axon at 3.5°C and in the absence of permeant cations . The holding potential was -70mV and the gating current is measured here at 0mV. Below is shown the sodium current from a squid axon in artificial sea water at the same temperature and voltage. (Reproduced from Armstrong & Bezanilla (1973) © 1973 Nature Publishing Group).

6 Hamill OP, Marty A, Neher E, Sakmann B & Sigworth FJ (1981). Improved patch-clamp techniques for high-resolution current recording from cells and cell-free membrane patches. *Pflügers Archiv* 391: 85-100

This is a paper concerned with method, and some are a bit sniffy about methodological papers. But patch clamp revolutionised electrophysiology and brought it into the mainstream of biological sciences. The 1970s saw electrophysiology a bit in the doldrums, at least in the UK, and the late Ebbe Petersen once told me that someone (who shall remain nameless) in a very senior position in the administration of UK science had told him that 'electrophysiology no longer (had) anything to contribute to new knowledge'. This statement was made in 1981 by someone who failed to notice a renaissance under way. Neher & Sakmann and their collaborators, including people like David Colquhoun and Alan Hawkes who pioneered the treatment of channel kinetics, also did a great job of widening access to the method, partly through their book on *Single-Channel Recording* (1995) and in many other ways. Getting your first seal in the 1980s was actually quite thrilling.

7 Hoshi T, Zagotta WN & Aldrich RW (1990). Biophysical and molecular mechanisms of *Shaker* potassium channel inactivation. *Science* 250, 533-538

This paper described what has now come to be known as N-type inactivation and is a most elegant experimental approach relating structure to function in *Shaker* channels, which activate and then rapidly inactivate under depolarisation. The findings only partly fulfil Clay Armstrong's prediction that a TEA^+-like metabolite would move into the pore to prevent K^+ ion flux. Rather, a cytoplasmic domain interacts with the open channel to cause blockage, though the principle is remarkably similar to what Armstrong had proposed (see above). As its name – N-type inactivation – tells us, the N-terminus is the domain involved. Its digestion with trypsin abolishes inactivation as does truncation of the N-terminus or appropriate mutation. The first 19 residues might be thought of as forming an inactivating ball, with the next 64 residues tethering it to the channel. Deletions of or insertions into the tethering sequence have the effect of speeding or slowing inactivation.

8 Kubo Y, Baldwin TJ, Jan YN & Jan LY (1993). Primary structure and functional expression of a mouse inward rectifier potassium channel. *Nature* 362, 107-108

The choice of this among the many wonderful papers that have come out of the Jan laboratory reflects my private passion for Kir channels – channels that set the resting potential of skeletal muscle and other cells and that are gated by both voltage and $[K^+]_o$. The paper describes the cloning of IRK1 or Kir2.1 from mouse macrophage. It was the second paper to describe a potassium channel with a different structure to that of voltage gated channels, but it confirmed the existence of a new family. As well as the molecular biology, there is clear electrophysiological analysis of the expressed channel protein, demonstration of its distribution in various tissues, and a correct prediction of the membrane topology. For better

or worse, I used the information from this paper to move my laboratory into the use of molecular approaches to channel function.

9 Lopatin AN, Makhina EN & Nichols CG (1994). Potassium channel block by cytoplasmic polyamines as the mechanism of intrinsic rectification. *Nature* 372, 366-369

If Clay Armstrong was only partly right about how K^+ channels might inactivate, he was pretty accurate in his prediction as to how Kir channels are gated. Excision of patches containing Kir channels resulted in loss of channel gating by voltage and $[K^+]_o$, but moving the patch back close to the oocyte from which the patch had been torn restored gating. Soluble factors were therefore important and these turned out to be polyamines, including spermine. These blockers move into the channel under depolarisation but are repelled from their blocking site by extracellular K^+ ions. We had established that an aspartate residue in the inner part of the pore was important to gating (Stanfield *et al*. 1994), and had thought it a voltage sensor. Instead the residue was important as part of the receptor for spermine.

10 Doyle DA, Cabral JM, Pfuetzner RA, Kuo A, Gublis JM, Cohen SL, Chait BT & MacKinnon R (1998). The structure of a potassium channel: molecular basis of K^+ conduction and selectivity. *Science* 280, 69-77

Finally, though it is still from the last century, I choose the solution of the structure of a bacterial potassium channel, KcsA. This confirmed early ideas about how potassium ion channels select. The 'narrow tube or channel' through which ions move has the kind of diameter Hille had predicted, and is lined with carbonyl oxygens as Bezanilla & Armstrong (1972) had also predicted in the 1970s. The selectivity filter contains two or three K^+ ions at any one time (Fig. 3). The structure was described as an inverted tepee, and the apex of the tepee is what is opened and shut to permit or prevent the movement of permeant ions. All this understates the achievement of crystallising and solving the structure of a membrane protein.

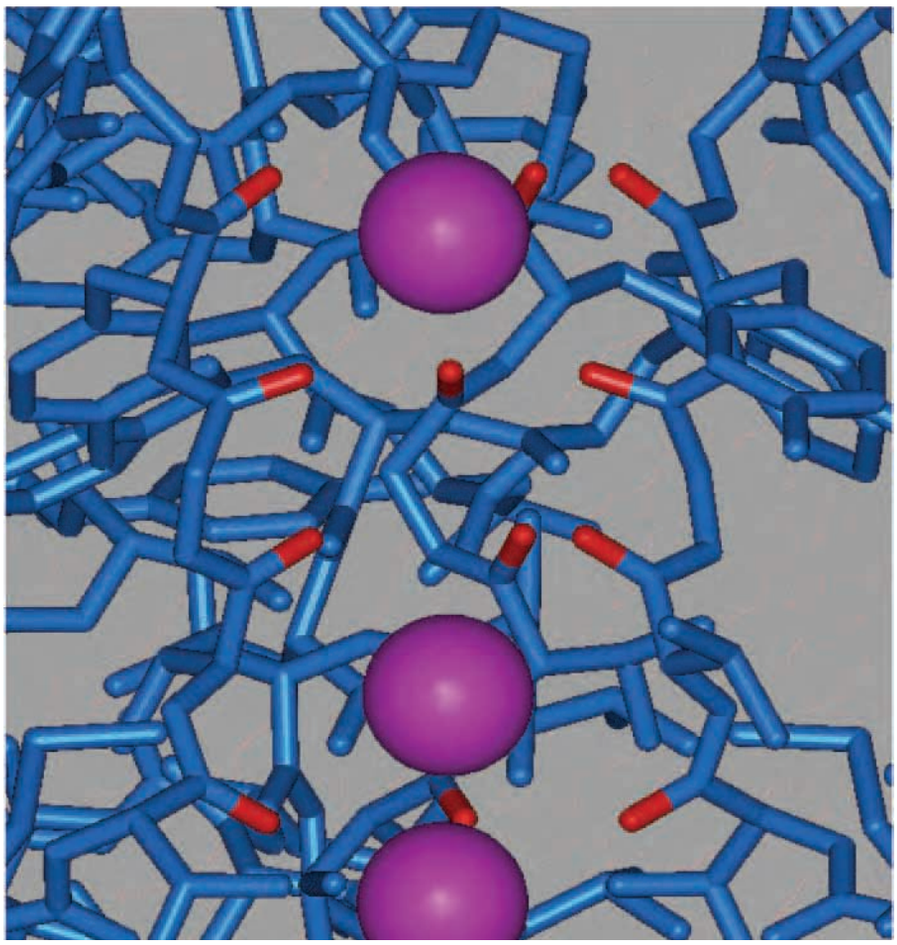


Figure 3. The selectivity filter of a K^+ channel as revealed by X-ray crystallography. The channel subunit immediately in front of the reader has been removed to show the lining of the filter. K^+ ions were confirmed as moving in single file through a series of binding sites formed by the backbone carbonyl oxygens (red) and the hydroxyl of a Thr side chain in the sequence (from intracellular) TVGYG. Extracellular is at the top. Three K^+ ions are shown, though the two lower sites are unlikely to be filled simultaneously, owing to electrostatic repulsion. A water molecule occupied the space between the two uppermost K^+ ions in the original description (Fig. 8 of Doyle *et al*. 1998). K^+ permeates in part because of its neat fit. Na^+ is too small and Cs^+ too big. Rb^+ can make it however. Figure courtesy of Michael Sutcliffe, University of Manchester.

MacKinnon was awarded the Nobel Prize for Chemistry in 2003 and Armstrong, Hille & MacKinnon the Lasker Prize for Basic Medical Research in 1999.

Peter Stanfield
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Coda

As Richard Naftalin pointed out in his contribution (2005), this series seems to be The Physiological Society's equivalent of *Desert Island Discs*. So perhaps, if forced, I have to make one choice. To take with me to a desert island, however, I would have to choose music rather than science. So, Mozart's *Marriage of Figaro* – Act 2 if I could have only part of it.

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What can clinical medicine give back to physiology?

John Dickinson gives a personal account

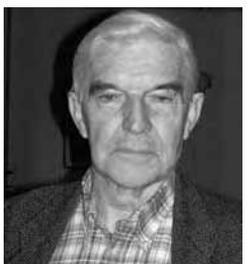
At school I was lucky to have had an inspiring biology teacher who got me interested in animal physiology. At Oxford my tutors were David Whitteridge and Hugh Sinclair, both of whom were medically qualified. Both said that exposure to clinical medicine had helped them understand physiology. They also pointed out (wryly) that a medical degree was useful for getting good preclinical jobs in medical schools. Both recommended University College Hospital for clinical training. But before I left Oxford, David invited me to spend a research year in his lab, working on vagal afferents related to distension pressures in cats' atria.

David encouraged me to make all my own equipment. This had to include a sensitive capacitor manometer, associated circuitry, high gain amplifiers and recording equipment. The experience hooked me into a physiological career. But later on I became equally fascinated by clinical medicine, and found that I really enjoyed looking after patients. This leads me to my first example of the type of contribution that clinical medicine can make to physiology.

'Essential' hypertension

When I became Max Rosenheim's house physician at UCH I looked after many of Max's patients with high blood pressure and wanted to find more about this strange condition. Most patients were diagnosed as having 'essential' hypertension, i.e. high blood pressure of unknown cause.

I read all the hypertension literature I could get hold of. The most potentially relevant early animal work had been done by Harvey Cushing, around 1900. He was later to become the world's most famous neurosurgeon, but in his early days he had done some physiological experiments. He observed that when he compressed the brain of a dog, to make it ischaemic, the blood pressure went up. This phenomenon has been known ever since as the 'Cushing response'. Twenty-five years later his



John Dickinson

observations stimulated Ernest Starling to note that high blood pressure could result from 'gross lesions of the arterial trunks (which) might diminish the average arterial pressure in the circle of Willis or in the small arteries of the brain. This condition is well known' (Starling, 1925). But at around the same time Corneille Heymans discovered the systemic arterial baroreceptors. These could detect and correct any fall of blood pressure. The Cushing response seemed not to be needed to protect the brain's blood supply. And in the late 1940s Seymour Kety devised a clever and non-invasive way of measuring cerebral blood flow in man. He reported that it was normal in essential hypertension.

Attention then turned towards the kidney. People with longstanding hypertension usually had small fibrosed kidneys. Harry Goldblatt had noted the widespread narrowing of the afferent glomerular arteries in people who had died with longstanding hypertension. He simulated this by putting constricting clips on the main renal arteries of dogs. This produced sustained hypertension, which closely resembled human essential hypertension. The idea for this brilliant physiological experiment came from clinical medicine.

Ischaemic kidneys were found to secrete the hormone renin, which acted on a circulating precursor to produce angiotensin. This was later identified and characterised by Stan Peart – a clinician working in a department of medicine. Angiotensin raised blood pressure spectacularly when infused into a vein. By the time I qualified in medicine in 1952, the aetiology of human high blood pressure seemed to have been largely sorted out.

My scientific career was interrupted by a year at UCH as Resident Medical Officer, in administrative charge of medical and surgical admissions. This gave me an unrivalled experience of acute medicine and surgery. Then followed 2 years in the British Army as a medical officer and junior medical specialist. I had time to read widely and to think more about essential hypertension. This gave me my first physiological idea, which came by thinking about human disease. The idea was ludicrously simple: perhaps the normality of cerebral blood flow in essential hypertension simply meant that the human brain had been successful in getting and keeping an adequate blood flow for itself – by raising systemic blood pressure – despite some obstruction to the brain's blood supply. Atheromatous deposits are widespread in the larger arteries of human adults. They usually narrow the arterial lumen and must impede blood flow in some measure. Was it even possible that essential hypertension could actually be the body's response to increased cerebrovascular resistance?

I wanted to test this idea, but I knew from the literature that it was fiendishly difficult to keep large cerebral arteries in animals constricted or clamped, to see whether this would make blood pressure rise and reach the stable operating condition that I had envisaged might comprise essential hypertension. Collaterals vessels always opened up in animals. Blood pressure soon went back again to normal levels.

But clinical medicine could provide a different approach. In hospital post-mortem rooms I had often seen people whose main cerebral arteries were narrowed or occluded by atheroma. On leaving the Army I was appointed a medical registrar at the Middlesex Hospital. I had access to the post-mortem room there and was lucky to meet a friendly, interested and cooperative pathologist (the late Drew Thomson). His charm bewitched the post mortem room attendants, who helped us. They gave us time and facilities to study nearly 100 cadavers.

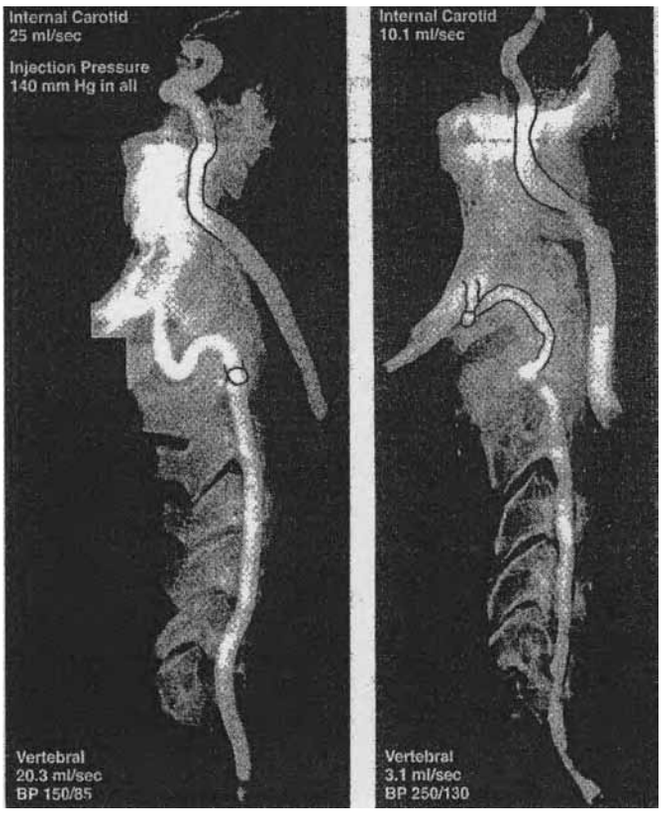


Figure 1. X-rays of the main brain arteries on one side of the neck removed from two human cadavers, showing the routes of the two arteries in relation to the bones of the neck (vertebrae) and the base of the skull. The vertebral arteries take a twisting looping course from their origin at the top of the chest to their termination inside the skull (at the top of the x-rays). *A*, shows a normal vertebral and internal carotid artery in a 43 year old woman with a near normal blood pressure. B, is from a woman of 59 with severe hypertension and gross stenosis of both arteries by atheroma. The perfusion rates for each artery were measured, then a hot solution of gelatin containing x-ray-opaque barium sulphate powder was pumped in and allowed to set while a pressure of 140 mmHg was maintained until the x-rays had been taken. Reproduced from Dickinson (2005).

All these former patients of the hospital had ante-mortem blood pressures recorded in the hospital notes – fortunately before hypotensive drugs had come along to confuse the picture. Another friend (Jack Howell) kindly read all the relevant hospital notes and independently recorded a value in each case which he thought best represented what had been the average ante-mortem blood pressures of each of our subjects. After each cadaver's skull had been opened and the brain removed, we dilated the four main cerebral arteries in the neck with dilute ammonia (to relax post mortem arterial spasm). Then we cannulated the proximal ends of each vertebral artery in the upper chest, and the origins of the two internal carotid arteries in the neck. Using a measuring jug held within the skull, and a stopwatch, we measured the maximum rate that water flowed along the length of each artery from a high reservoir providing a constant perfusion pressure of 140 mmHg.

Our results surpassed my wildest dreams.

In our crude measuring system, the flow resistance of the neck arteries varied over a more than 10-fold range. When the flow rates of the two vertebral arteries were taken together their average effective resistance was closely and directly related to each individual's ante-mortem blood pressure. The relationships were less for the two internal carotid arteries, and less still for the two femoral arteries in the same cadavers, perfused by the same technique (Dickinson & Thomson, 1960). The main renal arteries were too short to perfuse, but we estimated their maximum diameter with graduated round glass rods. There was some (inverse) relation of renal artery diameter to ante-mortem blood pressure, but nothing to suggest that main renal artery stenosis was a frequent or important cause of human hypertension.

Two examples of the two main cerebral arteries which we examined are shown in Fig.1. Each vertebral and internal carotid artery has been tied at its distal end and filled with a hot suspension of powdered barium sulphate in gelatine, held at an injection pressure of 140 mmHg until the gelatine had set. Both arteries illustrated on the right show many areas of gross atheromatous stenosis.

These observations did not, of course, prove that cerebral vascular disease caused human essential hypertension, but they were compatible with my idea. They provided a starting point for further research.

With a Rockefeller Travelling Fellowship, awarded by the MRC, I pursued the Cushing response in dogs, in Jim McCubbin's department in the Cleveland Clinic Research Division. Jim and I observed that the response was almost eliminated by general anaesthetics, but that the brain stem of conscious or only lightly sedated dogs could increase sympathetic vasoconstrictor tone and blood pressure when made ischaemic (Dickinson &McCubbin, 1963). Since then an exquisitely sensitive Cushing response has been reported in unanaesthetised fetal sheep, *in utero* (Harris *et al*. 1989). I have been kept awake with excitement recently by hearing from Julian Paton, in Bristol, of his work on single chemosensitive neurones in the brainstems of decerebrate rats. He is engaged in a comprehensive study of the neural organisation of the mammalian brainstem, with particular reference to chemosensitive structures serving the autonomic nervous system.

These adventures in clinical physiology led to many original papers and to my two monographs on *Neurogenic hypertension*, one published by Blackwell in 1965 and the other by Chapman & Hall in 1991. Fellow hypertensiologists remain mostly sceptical, though none has so far disproved my idea – which is surely the best that any scientist can hope for. And there is increasing and widespread general interest in neurogenic theories of human hypertension.

The progressive pressor response to small amounts of angiotensin

I have already said that angiotensin raised systemic arterial pressure when it was infused intravenously. After sensitive analytical methods had been developed for measuring renin and angiotensin concentrations in blood, a problem appeared. Although intravenous infusions of angiotensin into human subjects could raise the blood pressure, there was not nearly enough angiotensin circulating to account for the sustained hypertension of people with obvious 'renal' causes of hypertension, e.g. those with severe stenosis of a main renal artery.

Could a physiological approach solve the problem? Perhaps the same type of reasoning which I applied to increased cerebrovascular resistance causing human hypertension might help. Once blood pressure had stabilised at an elevated level, further angiotensin might not be needed to keep it there. Control systems might have been reset. Jim McCubbin and John Green had observed that the carotid artery baroreceptors of dogs with chronic renal hypertension had reset themselves to operate at and sustain the higher blood pressure level (McCubbin *et al*. 1956). So I devised a piece of machinery which continuously measured the arterial blood pressure of a rabbit and controlled the rate of administration of synthetic angiotensin. My servo manometer controlled three different intravenous infusion rates of angiotensin, in inverse proportion to the current level of my rabbit's blood pressure.

The results were immensely exciting. Jim Lawrence and I first raised a rabbit's blood pressure 30-40 mmHg by infusing angiotensin at a moderately high rate. Then we switched on the servo system. Although blood pressure remained at the high level we had set the control system to maintain, the infusion rate of angiotensin steadily declined over the next 3 days until it was only about 5% or less of the rate initially needed to sustain hypertension. This result stimulated us to perform the obvious and much simpler experiment.

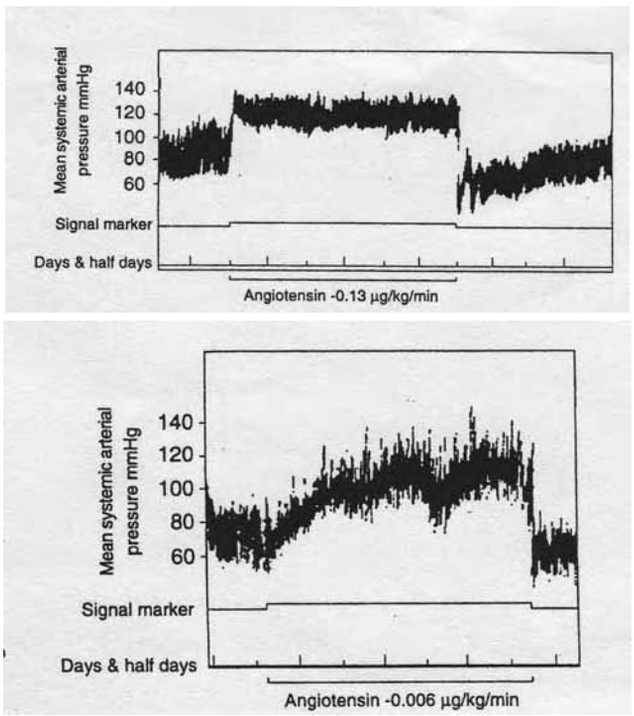


Figure 2. *Top*, a 6 day record of the mean blood pressure of a rabbit made with a servo-manometer. During the 3 days indicted by the signal marker angiotensin II was infused intravenously at a high constant rate. The blood pressure went up rapidly by about 40 mmHg, remained steady for 3 days, then dropped immediately when the infusion was stopped. Damped oscillations with a 4 h period continued as the blood pressure slowly returned to its control level over the ensuing 2 days. *Above*, a 4-5 day record made in the same way, but showing the contrasted and different effect of infusing a *low* concentration of angiotension at a rate which had no immediate effect on blood pressure. The average blood pressure slowly climbed up by about 35 mmHg over 3 days, but dropped sharply when the infusion was turned off. Reproduced from Dickinson (2005).

We continuously infused very low concentrations of angiotensin into rabbits, and saw blood pressure rise steadily over some 3 days to a level as high as that which was immediately reached by the acute infusion of angiotensin at concentrations twenty or more times higher (Dickinson & Lawrence, 1963). Fig. 2 compares the blood pressure responses to 3 days intravenous infusion of synthetic angiotensin II into a rabbit at constant rates of 0.13 and 0.006 $\mu g.kg^{-1}.min^{-1}$. Our observations seemed to explain in a convincing way how angiotensin could cause human renal hypertension despite there being only minute amounts of the hormone in the blood.

Conclusion

I have been delighted by the striking success of the original hypothesis, and the other which I have described. Whether they eventually prove to be right or wrong, they have brought clinical observations and physiology together in mutually satisfying ways. I am proud to have been a 'clinical scientist', and to have been able to describe, study and, occasionally, account for some 40 more clinical and fascinating *Medical mysteries*, always from a physiological standpoint (Dickinson, 2005).

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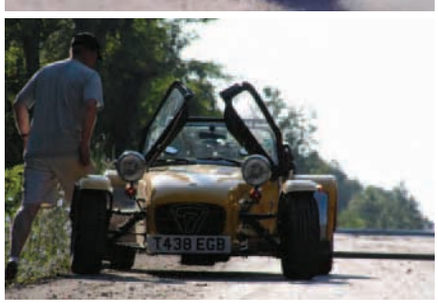
In a future issue, John Dickinson continues this account with another clinical/physiological example: *Fainting: a 'most intriguing mystery in cardiovascular physiology'*.

Frivolous days in the life of physiologists having fun

Christof Schwiening and Andy Newport discover the true significance of low TRH



Having flown over one of these ridges I slammed on the brakes – now we had two more to negotiate. The oil sump sticks out under the car (just behind the number plate) about 4 inches from the road surface – one knock could finish the trip.

We had overtaken these carts about 15 min before, now we were stuck working out how to get over an area of poor road.

A pressure wash in Turkey after going through mud-covered roads in Bulgaria. At this point the car was clean, and the garage mechanic was eager to do an engine/oil check. With the police watching and taking pictures, we felt sure he would do a good job! I was a bit worried about taking this picture of the police, and just after it they stiffened up.

During the first few minutes of 2006, in a moment of recollectable merriment, I agreed to accompany an old friend (Andy Newport, who did a PhD at Bristol with the late Don Lewis) on a road trip. Unfortunately, the following morning, before I could wriggle out of it, my wife had scornfully dismissed the idea at the breakfast table. In the cold light of day I had considered the permanent postponement of the trip the best option, but there is hardly a more potent stimulus than scorn to harden one's resolve.

The road trip was ostensibly a last farewell for a fellow physiologist's investment – a bright yellow sports car purchased in more affluent times – before it was transmuted from base metal to gold and placed in the pockets of builders. By February plans for a trip around the Mediterranean or to the Artic circle had been replaced by a mad dash to the Black Sea and back – maybe even into Asia via Istanbul. Whilst I had driven to Warsaw in 1991 I was unfamiliar with much of Eastern Europe – beyond Prague.

Thus, we began to make plans – insurance, breakdown cover, accommodation, currencies, maps etc. It is not easy to insure a sports car for much of Eastern Europe – indeed Serbia, Bosnia and the Ukraine, amongst others, proved to be impossible. Then in May we realized – in a rare moment of lucidity – that I had never driven a sports car – could I do it? My 16 year old Volvo can be safely driven with the right foot flat to the floor for minutes on end. However, Andy's Caterham was a different matter – something I found out much later. The 1.8 L Rover engine is light, freely revving and prone to stalling – the driving position could be best described as low and laidback. Andy brought his car to Cambridge from near Bristol and I had a go. My first challenge was to reach the pedals: slouching as instructed, I could hardly see over the ridiculously long bonnet. It was raining that day, so my progress was slow – I

Zigzagging up through the Alps without any doors – loud, but extremely good fun.

Above: Repairs. Earlier that day on the motorway I had tried to clean the windscreen using the wash-wipe system. All I managed to do was squirt Andy in the face with hot water as the tubing below the dashboad blew apart. It was now my job to get in there and fix the leak.
Below: Nice legs, but just a bit too small for our Part I practicals!

Apparently you can squeeze a couple more litres of fuel into your tank if you jack up one side of your car.

may actually have reached 40 mph at one point. But my performance was just good enough to allow our plans to continue.

We had decided that we would also try and raise money for a lightweight new leg for Nikki Britton, who had lost one of hers in a car accident. The story was particularly tragic since the accident occurred as her brother was attempting to rescue her after she slid off the road in icy conditions. Thus, we began collecting sponsorship.

At 4.30 a.m. on 30 June we were off. Initially I took the role as navigator and soon began to regret my earlier enthusiastic start to the day – two cups of strong coffee – as I sat uncomfortably contemplating the likely trajectory for orally ejected fluids in an open topped car. We took the tunnel across to France, and sped through Belgium and Germany putting considerable distance between us and Andy's credit cards (that's another story!) …

In Germany I took over the driving. Much to my surprise, I found that the car wouldn't go much faster than 120 mph before the rev limiter cut in. However, it accelerated faster than anything else on the road – if there was sufficient grip! The lack of decent aerodynamics caused the fuel consumption to increase dramatically when cruising at speed – and the noise was horrendous. The wind constantly threatened to rip anything held above waist height out of the car. Fortunately, there was little to hand to lose, other than the GPS, since the cockpit was incredibly cramped and the seat harness held us firmly in place. Whilst the lack of space in the cockpit was inconvenient, the small fuel tank was a blessing, making frequent stops a necessity. It was impossible to eat or drink whilst driving.

We took 5 days to get down to Istanbul (France, Belgium, Germany, Czech Republic, Slovakia, Hungary, Romania, Bulgaria, Turkey), and then 5 more to get back (Turkey, Bulgaria, Romania, Hungary, Austria, Switzerland, France). We camped most nights, except for one stay in a hotel, and another in a monastery. It was, without doubt an adventure – my diary for half the trip covers over a dozen pages: pot-holes the size of coffee tables, on-coming lorries on the wrong side of the road, metal-rimmed horse-drawn carts, main roads with the surface of farm tracks, solitary tower blocks in the middle of the countryside, ludicrous local taxes at borders, the smell of chips from diesel engines, the ravages of communism, glaciers and men with rough chins breathing the word 'money' just too close.

Andy's Serbian brother! He had just given Andy a nice kiss – I don't think Andy was expecting that! They exchanged telephone numbers despite having no language in common ...

Above: At the top (~2.5 km high) of the Grossglockner Hochalpenstrasse we found a small, steep road with a no entry sign. After a quick reconnoitre we headed straight up it in first gear. In the background you can see the glacier making its way slowly down the mountain.
Below: A Romanian campsite. Perfect – quiet with soft ground, but we had to cook by torchlight.

I am glad I went. The bug-eyed Caterham, with a testicular ride height (TRH) of only a few inches, was the perfect car for a trip down to Istanbul – both reliable and silly enough to cause nearly everyone to smile.

We got back in one piece having had the most amazing set of experiences in rapid succession. My lasting memories are of laughing faces, toothless grins, the vast differences between people and places only a few hundred miles apart and the willingness of strangers to help if asked.

In the end we raised a total of £2,300 for Nikki's leg – many thanks to all of you who contributed.

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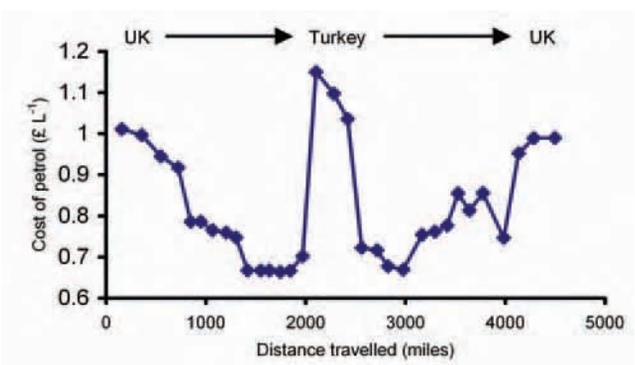
See outside back cover for more images of Christof's epic road trip



Trans-European fuel costs plotted in sequence from UK to Turkey and back to the UK. Fuel was very cheap in both Romania and Bulgaria, but not in Turkey. From the horizontal spacing between the data points you can see that after the fourth refuelling we stopped more frequently (141±34 miles, putting in 18.3±5.0 L, n=33) — largely because we were almost stuck on the motorway with an empty tank. The fuel tank was about half the size of that found in a normal small car (29 L) and the fuel gauge was hopelessly inaccurate. In total we bought 134 gallons of petrol costing just over £500.

Afferent impulses in the vagus and their effect on respiration

John Widdicombe launches our occasional series of highlights from *The Journal of Physiology* online archive with a critical look at E D Adrian's classic 1933 paper

E D Adrian's 1933 paper is rightly regarded as a classic. It is over 50 years since I first read it and I have frequently quoted it and regarded it as magnificent (correct) and almost beyond criticism (wrong). He was the first to do afferent single-fibre recording from the vagus nerve and thus inspired a plethora of similar studies, still continuing today. He was one of the first to use the cathode-ray oscillograph, soon to be replaced by the oscilloscope. The technical difficulties must have been formidable.

Adrian established the afferent pathway for the Hering-Breuer inflation reflex that originates in pulmonary stretch receptors and controls the pattern of breathing, and described its characteristics. Until his paper there was still some dispute as to the nature and significance of this reflex. After his paper there was little argument. His illustrations show, for the first time, beautiful single-fibre nerve impulses from vagal afferents (Fig. 1). The only previous records of vagal activity were multifibre; some looked like wind-swept sand dunes and others like seismographs of a Richter Scale 1 earthquake. After his paper every reviewer of respiratory neurophysiology quotes him first in their alphabetical reference list (if I am quoted it is usually last, a just position based on our relative distinctions).

The paper displays a precious jewel, both valuable for its insight into lung reflexes and beautiful for the elegance of Adrian's expertise and experimental techniques. But the gem is mounted in a rather unworthy setting. Adrian lists 16 references, of which only five are relevant to vagal respiratory reflexes. The others are concerned with his interest in non-vagal somatic reflexes. Later reviews, e.g. Coleridge & Coleridge (1964), list over 40 references published before 1933 which are directly relevant to Adrian's paper. Of course I am not suggesting that he should have written a review article, but only that he should not have omitted papers basic to his thesis. He does say 'a brief discussion cannot hope to do justice to earlier work', and then goes on with 11 pages of discussion! Amazingly he does not refer to Breuer's paper in 1868, the foundation of our understanding of the Hering-Breuer inflation reflex and the basis of Adrian's study; nor does he mention the reflex as so-named. He completely misses the point of two important papers he cites. Head (1899) established that the 'deflation reflex' had an afferent pathway different from that of the inflation reflex of Breuer; collapse of the lungs caused a stronger inspiratory reaction than cutting the vagi, and therefore the phenomenon could not have been due solely to removal of the inhibitory pathway for the inflation reflex. Breuer had suspected this but not proved it. But Adrian, who described 'deflation fibres', does not relate them to the 'deflation reflex', which he does not mention; its afferent pathway was only analysed many years later. He cites Keller and Loeser (1929) but misses the point that they recorded from vagal fibres from 'deflation receptors' and concluded that they mediated cough, the most powerful of all the pulmonary vagal reflexes; Adrian does not mention cough. However, Adrian was loyal to his university (Cambridge) and its printing house (CUP); 12 of the 16 papers he cites were in *J Physiol*.

Let me be emphatic; this is a very important paper that stimulated much research and led to better understanding of respiratory reflexes. But a critical reviewer might have asked Adrian to study the literature more closely, and to relate already published results to his own new findings. I assume that Adrian's reviewers were not influenced by the fact that he had received a Nobel Prize (shared with Sherrington) the previous year, and that he was on the Editorial Board of *The Journal of Physiology*!

This paper was one of a series in which Adrian studied afferent pathways in many mainly somatic nerves. He published many papers on this topic in the years 1929–1934 alone but subsequently no more on vagal reflexes. The papers were a turning point in neurophysiology and contributed to a great career which made him one of the most distinguished physiologists of the last century.

His neglect of the literature was shared by another great British neurophysiologist, Charles Sherrington; in the *Integrative action of the nervous system* (1906) he devotes only six lines to the Hering-Breuer inflation reflex, although it was one of the best-established examples of negative feedback, and only three lines to Head's paradoxical reflex, an established and rare example of positive feedback.

If Adrian could not maintain an interest in vagal reflexes he was in good company. Breuer, Head and Kratchmer (upper airway reflexes) (1870) each published essentially a single paper on the subject, which laid the foundation of airway and lung reflexes, and each then went on to achieve great distinction in other fields. A wonderful quartet!

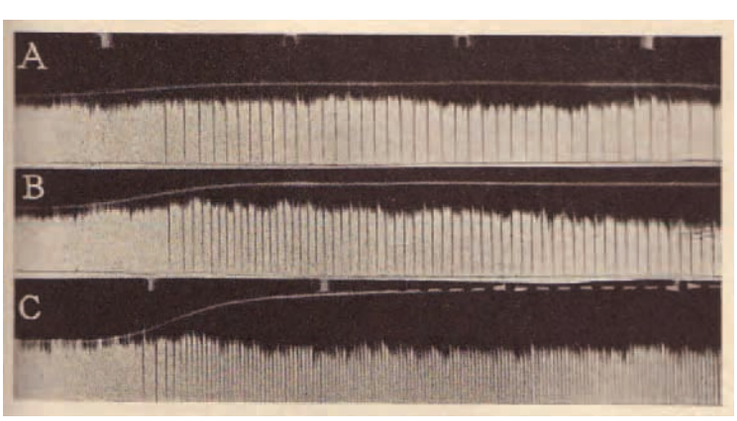


Figure 1. Record from single fibre of vagus (decerebrate cat) showing discharges at different lung inflations by pump. *A* 65 ml, *B* 115 ml, *C* 230 ml. Upper trace moves upwards on inflation. From Adrian (1933).

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Reactive oxygen species and glucose transport during exercise

Glucose transport is an essential metabolic event that is characteristic of all eukaryotic cells. With respect to skeletal muscle, contraction is the most potent physiologic stimulus for glucose transport, resulting in up to a 50-fold increase during maximal exercise in humans (Katz *et al.* 1986). Whereas the full sequence of reactions underlying the activation of glucose transport during exercise has not been elucidated, there is good evidence that the activation of AMP-activated protein kinase (AMPK) plays an integral role in this process (Hardie & Sakamoto 2006).

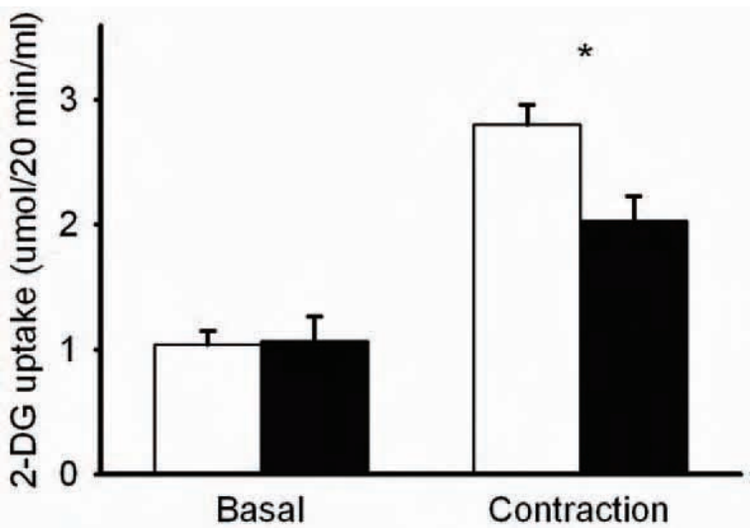

Figure 1. NAC inhibits contraction-mediated glucose uptake in mouse EDL muscle
Values are means±SEM for 6-8 muscles. Unfilled bars, control; filled bars, NAC (20 mM). *P<0.05 vs control.

Reactive oxygen species (ROS) consist of the superoxide anion and several of its derivatives, including hydrogen peroxide (H_2O_2). Skeletal muscle produces ROS at a low rate in the basal state and markedly higher rates during exercise (Murrant & Reid, 2001). Considering the evidence that exogenous ROS stimulate glucose transport in skeletal muscle and that contraction stimulates ROS production, it would seem intuitive that endogenous ROS production would play an important role in contraction-mediated glucose transport. Indeed this hypothesis was recently made, following the observation that addition of exogenous H_2O_2 to isolated muscle preparations at rest resulted in the activation of glucose transport and AMPK (Toyoda *et al.* 2004).

Now, we have tested this hypothesis (Sandström *et al.* 2006). Fast-twitch, extensor digitorum longus (EDL) muscles were isolated from mice and incubated in a physiological salt solution. The muscles were then stimulated to perform repeated contractions and analyzed for glucose uptake. Repeated contractions increased glucose uptake almost 3-fold, as measured with the glucose analogue: 2-deoxyglucose (2-DG) (Fig. 1). If the muscles were exposed to a general antioxidant, N-acetylcysteine (NAC), the contraction-mediated glucose uptake was diminished by about 50%. This indicated that endogenous ROS production played a significant role in contraction-mediated glucose uptake. To assess whether the NAC effect was specific for contraction, additional modes of glucose uptake activation were investigated. However, NAC did not affect insulin or hypoxia-mediated glucose uptake (Sandström *et al.* 2006). This suggested that the ROS involvement in glucose uptake was specific for exercise and not other physiologic stimuli.

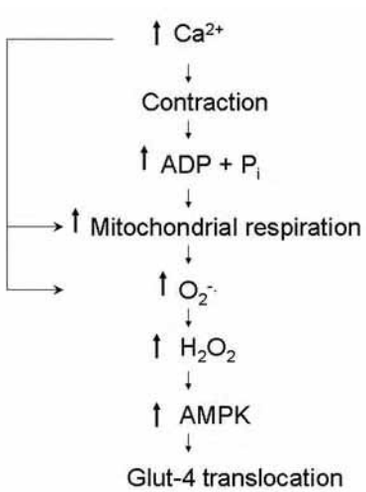

Figure 2. Scheme for ROS-mediated glucose transport during muscle contraction Following the release of Ca^{2+} from the sarcoplasmic reticulum, actomyosin interaction occurs resulting in muscle contraction, ATP breakdown and ADP and P_i increases. ADP and P_i stimulate mitochondrial respiration, which can also be stimulated by increases in Ca^{2+} that activate mitochondrial dehydrogenases. Increased respiration results in superoxide anion ($O_2^{\cdot-}$) formation through NADH dehydrogenase and semiquinone components; $O_2^{\cdot-}$ formation can also occur by extramitochondrial mechanisms (eg., via a Ca^{2+}-mediated activation of phospholipase A_2). $O_2^{\cdot-}$ is then dismutated by superoxide dismutase to H_2O_2, which results in increased LKB1-mediated phosphorylation and activation of AMPK, followed by a translocation of Glut-4 to the surface membrane and an increased glucose transport.

To establish that the NAC effect was associated with ROS metabolism, additional experiments were performed. We found that both intracellular ROS accumulation and alterations in glutathione status (reflects increases in ROS production) were blocked by NAC (Sandström *et al.* 2006). Thus NAC was functioning as an anti-oxidant.

To confirm the species of ROS involved in contraction-mediated

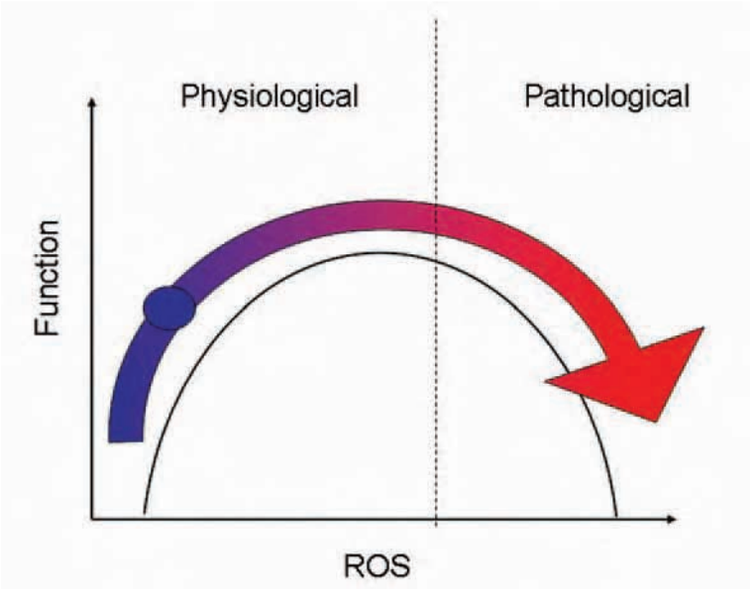

Figure 3. Scheme for biphasic relationship between cell function and ROS levels
Blue bulge on left denotes resting state. Relationship is based on a model regarding muscle function and cellular redox balance (Andrade *et al.* 1998).

glucose uptake, we performed two additional experiments. In one, we used another anti-oxidant, ebselen, which functions as a glutathione peroxidase mimetic that removes H_2O_2 in the presence of reduced glutathione (GSH). Ebselen also inhibited contraction-mediated glucose uptake and to an extent similar to that seen with NAC (Sandström *et al.* 2006). This suggested that the ROS species involved in contraction-mediated glucose transport was H_2O_2.

We also studied muscles from mice that over-expressed manganese-dependent superoxide dismutase, which is the mitochondrial isoform of the enzyme that converts the superoxide anion to H_2O_2. Assuming that the production of superoxide anion is not altered compared with the wild type condition, this would result in an increased production of H_2O_2 and hence an increase in contraction-mediated glucose transport. Indeed, muscles from mice over-expressing the enzyme exhibited a glucose uptake rate following contraction that was about 25% higher than in wild type muscles (Sandström *et al.* 2006). Taken together, these results indicated that either H_2O_2, or one of its derivatives, was the ROS species involved in the activation of glucose transport during contraction. Based on our recent results, as well as other information available in the literature, we proposed the sequence of events depicted in Fig. 2 to explain how ROS stimulate glucose transport during exercise.

To study the mechanism whereby ROS mediate their effect on glucose transport, we measured the activity/phosphorylation state of AMPK. We found that NAC also inhibited the contraction-mediated increase in activity and phosphorylation (represents activation) of AMPK by about 50% (Sandström *et al.* 2006). Thus the ROS effect appeared to involve activation of AMPK.

Generally, ROS are associated with negative effects on body function, including muscle fatigue (Medved *et al.* 2004). However, recent studies have also implicated ROS as essential signaling molecules for normal physiological processes. The apparent paradox may be resolved by considering that excessive levels of, or prolonged exposure to ROS exert deleterious effects on cell function and viability, whereas low/physiological levels appear to be requisite for proper cell signaling and function. To this, one can add the possibility that different species of ROS affect various metabolic/structural targets to varying degrees depending on the conditions studied. A scheme to depict this view is given in Fig. 3. To illustrate the point one can imagine a situation where excessive amounts of ROS are produced during heavy exercise resulting in premature fatigue (i.e. a decrease in cell function). In this situation anti-oxidants would be expected to delay fatigue and hence have a positive effect on cell function, as has been demonstrated elsewhere (Medved *et al.* 2004). However, in a situation where one relies heavily on glucose transport (eg, prolonged, submaximal exercise) and during which physiological amounts of ROS are produced, anti-oxidants could have deleterious effects.

So what can one conclude from the data? The conclusion is that, depending on the conditions, antioxidants can have either positive or negative effects on muscle performance.

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The amazing versatility of hPEPT1

hPEPT1 is the port of entry into enterocytes of all possible di- and tri-peptides resulting from the digestion of dietary proteins. Since the mid-1990s, it has been exploited as a tool to enhance the oral availability of an ever-increasing number of drugs and prodrugs –both peptidic and non-peptidic. Recently, Monica Sala-Rabanal and colleagues uncovered the molecular mechanism by which peptides and drugs alike make their way into the human enterocytes

The human proton-coupled oligopeptide cotransporter hPEPT1 (gene *SLC15A1*) is expressed in the brush border membrane of the enterocytes, the S1 segment of the renal proximal tubules and the hepatic bile ducts. In addition to being responsible for the uptake of all natural di- and tri-peptides, this all-purpose transporter has been implicated in the absorption of everyday drugs, such as β-lactam antibiotics. Here, I will highlight the milestones of oligopeptide transport research and review the key molecular, functional and pharmacological aspects of hPEPT1.

Monica Sala-Rabanal

The search

The first evidence that intact peptides are transported across the intestinal epithelium was obtained in the late 1950s (Newey & Smyth, 1959). Until the early 1970s, however, the predominant view was that dietary protein was absorbed primarily in the form of free amino acids. This was challenged when it was observed that patients suffering from genetically impaired amino acid transport, as occurs in cystinuria and Hartnup disease, did not develop protein malnutrition. *In vivo* absorption studies in human volunteers suggested the presence of a low affinity, high capacity transport system for di- and tripeptides, but that would not take longer peptides or single amino acids (see Adibi, 1997). During the 1980s, extensive work in intestinal brush border membrane vesicle (BBMV) preparations and the human colon cancer cell line CaCo-2 confirmed the existence and basic kinetics of the system, and unveiled key features of the mechanisms involved in short-chain peptide absorption. In particular, evidence collected by Leibach and coworkers on rabbit BBMV demonstrated that transport of di- and tripeptides is electrogenic and coupled to an inwardly-directed proton gradient (see Ganapathy & Leibach, 1985). A major breakthrough came with the expression cloning of the first mammalian gene that encoded peptide transport activity, the rabbit PEPT1 (Fei *et al.* 1994); cloning and functional characterization of the human isoform followed (Liang *et al.* 1995; Mackenzie *et al.* 1996b; Sala-Rabanal *et al.* 2006).

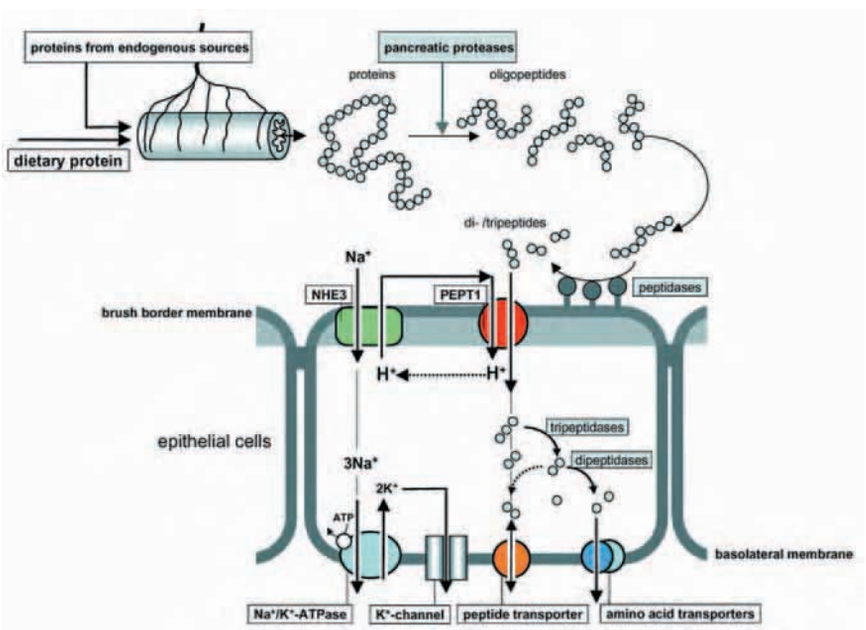

Figure 1. Model of intestinal peptide absorption. Dietary proteins are hydrolyzed by pancreatic proteases, and subsequently broken into short-chain peptides by peptidases in the apical membrane of enterocytes. Di- and tripeptides are transported into the cytoplasm by PEPT1, against a concentration gradient and with protons. Peptides are then released through an unidentified basolateral transporter or hydrolyzed by endogenous peptidases into amino acids, which then exit via specific transporters. The overall electrochemical balance is maintained by the apical Na^+/H^+ exchanger NHE-3 and the basolateral Na^+/K^+-ATPase (Daniel, 2004). (Reprinted, with permission, from the *Annual Review of Physiology* **66** ©2004 by Annual Reviews, www.annualreviews.org).

Mechanisms of hPEPT1 function

Fig.1 illustrates the standard model of intestinal peptide absorption. After a meal, proteins are hydrolyzed by pancreatic proteases, and subsequently broken into short-chain peptides by peptidases located in the apical membrane of enterocytes. Di- and tripeptides are then carried into the cytoplasm by hPEPT1, against a concentration gradient and together with protons. Peptides are then released unmodified to the blood –through an unidentified basolateral transporter– or hydrolyzed by the action of endogenous peptidases into amino acids, which then leave the cell via specific transporters. The overall electrochemical balance is maintained by the apical Na^+/H^+ exchanger NHE-3 and the basolateral Na^+/K^+-ATPase (Daniel, 2004).

To address the molecular mechanism of apical H^+/oligopeptide cotransport, we expressed the cloned hPEPT1 in *Xenopus laevis* oocytes and performed comprehensive voltage-clamp electrophysiological assays. We found that transport by hPEPT1 is electrogenic, H^+–coupled, and voltage dependent (Mackenzie *et al.* 1996b; Sala-Rabanal *et al.* 2006). hPEPT1 is capable of transporting neutral and charged substrates; in all cases, transport is associated with the generation of inward cationic currents, regardless of the net charge of the substrate (Mackenzie *et al.* 1996a).

In addition, hPEPT1 responds to step jumps in membrane potential with transient presteady-state currents or charge movements (Mackenzie *et al.* 1996a; Sala-Rabanal *et al.* 2006), that have been postulated to be due to changes in the conformation of the carrier protein as it goes through the transport cycle (Loo *et al.* 1993).

By simultaneous analysis of the kinetics of steady-state dipeptide-induced inward proton currents –to monitor substrate transport– and of presteady-state currents –to monitor the protein conformations during the H^+/dipeptide cotransport–, we established a kinetic model for hPEPT1 function (Sala-Rabanal *et al.* 2006).

The ordered model, summarized in Figure 2, assumes that cotransport happens through a series of conformational changes induced by the binding of ligands (H^+ and substrate) and membrane potential. In a transport cycle, one H^+ binds to the outside-oriented empty transporter (state C_1) to form the proton-carrier complex (C_2). Then the substrate binds, and the substrate-loaded protein (C_3) undergoes a conformational change (C_4) that results in H^+/dipeptide cotransport. On the cytoplasmic side, the substrate dissociates (C_5), and then the proton is released (C_6). A rate-limiting step of the transport cycle is the reorientation of the empty carrier within the membrane ($C_6 \rightarrow C_1$). Variations in dipeptide and drug transport by hPEPT1 are due to differences in affinity and in turnover rate.

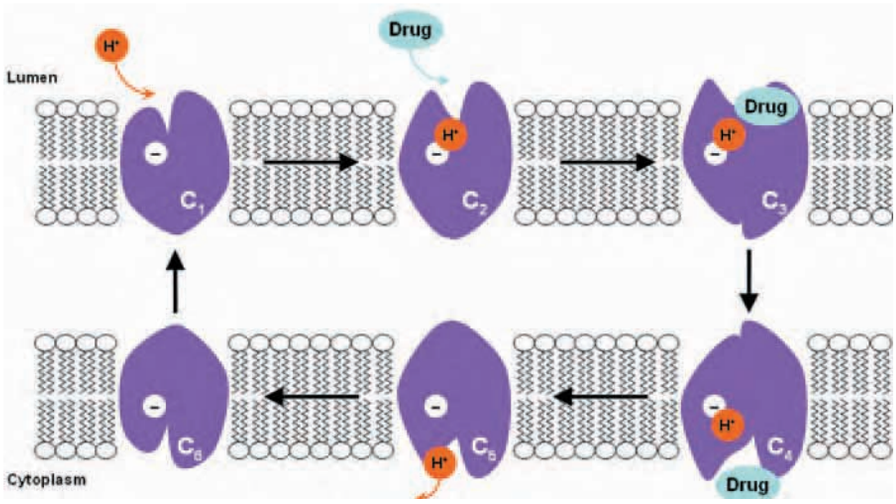

Figure 2. Schematic representation of the kinetic model for H^+/dipeptide cotransport by hPEPT1. The model assumes that the empty carrier is negatively charged. In a transport cycle, one H^+ binds to the outside-oriented empty transporter (state C_1) to form the proton-carrier complex (C_2). Then the substrate binds, and the substrate-loaded protein (C_3) undergoes a conformational change (C_4) that results in cotransport. On the cytoplasmic side, the substrate dissociates (C_5), and the H^+ is released (C_6). The partial reactions C1 ↔ C2 and C6 ↔ C1 are voltage-dependent, and are responsible for the electrogenicity of the transporter (adapted from Sala-Rabanal *et al*. 2006).

Surprising substrate selectivity: peptide bond not a must!

Over the last decade, the substrate specificity of hPEPT1 has been subject to intense scrutiny, driven by the prospect of using the transporter as a way to enhance oral bioavailability of drugs and prodrugs. Recently, comprehensive three-dimensional quantitative structure-activity relationship (3D-QSAR) studies have led to the identification of the minimum structural requisites for hPEPT1 substrates, among which, remarkably, a peptide bond is not included. Thus, the essential features for recognition comprise a simple three-point model: the presence of hydrogen-bond donor and acceptor sites and an electrodense region at given positions within the molecule are sufficient to grant access to the peptide transporter binding site (Biegel *et al*. 2005).

One direct implication of such unrestrictive steric requirements is that virtually all possible natural di- and tripeptides composed by L-α-amino acids may be transported by hPEPT1 – an impressive 8,400 different substrates. In addition, a large number of pharmacologically active compounds, both peptidomimetic and non-peptidic, satisfy the minimums and have been tested as putative hPEPT1 substrates. The list includes β-lactam antibiotics (penicillins and cephalosporins), inhibitors of the angiotensin-converting enzyme (captopril, enalapril), antineoplastics and prodrugs (valacyclovir).

Drug absorption and structure-affinity studies have been largely based on competition assays (Daniel, 2004; Biegel *et al.* 2005), mainly because these compounds are not commercially available in radiolabelled form. Competition assays, however, do not allow discrimination between substrates and inhibitors –that is, whether a given drug is transported or simply recognized and bound to the carrier. Using our electrophysiological approach, we demonstrated that β-lactams ampicillin, amoxicillin, cephalexin and cefadroxil, and the antineoplastics bestatin and δ-aminolevulinic acid are indeed transported by hPEPT1, by the same alternating-access mechanism as dipeptides (Fig. 2). These drugs are transported with lower affinity and turnover rate than dipeptides. Our findings implicate that drug absorption by hPEPT1 may be compromised by the presence of physiological concentrations of dietary peptides in the gut. Thus, oral delivery drugs should be taken on an empty stomach (Sala-Rabanal *et al.* 2006).

Future directions

Despite the unquestionable progress that has been made, there are still gaps in our knowledge about hPEPT1-mediated drug absorption. Given the pharmacological importance of hPEPT1, solving the crystal structure would validate and complement the computational studies and provide a gigantic leap towards the rational design of oral delivery drugs and prodrugs.

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Where is my arm?

The subject of proprioception is concerned with the body's ability to sense its own actions. One aspect that Uwe Proske, below, has been studying recently is the kinaesthetic sense, the sense of position and movement of our limbs

The present-day view for muscles acting about the elbow joint is that an important source of positional information comes from the muscle spindles of elbow flexors and extensors. We believe that muscle spindles signal muscle length. During rotation of the joint, as a muscle is stretched, spindle discharge increases in direct proportion to the size of the length change. In other words, signals of muscle length change are interpreted by the brain as movements about the joint. There are two pieces of evidence in support of the view that muscle spindles provide information about limb position. The first were the ground-breaking observations of Goodwin *et al.* (1972) who described illusions of movement and changed position of the elbow during vibration of elbow muscles. At that time it was already known that muscle spindles were exquisitely sensitive to vibration (Brown *et al.* 1967). The second observation supporting a role for muscle spindles as kinaesthetic sensors uses the muscle property called thixotropy. This is the change in passive tension of skeletal muscle following conditioning contractions and length changes. Since the intrafusal fibres of muscle spindles, on which the spindle sensory endings lie, also exhibit thixotropy, it means

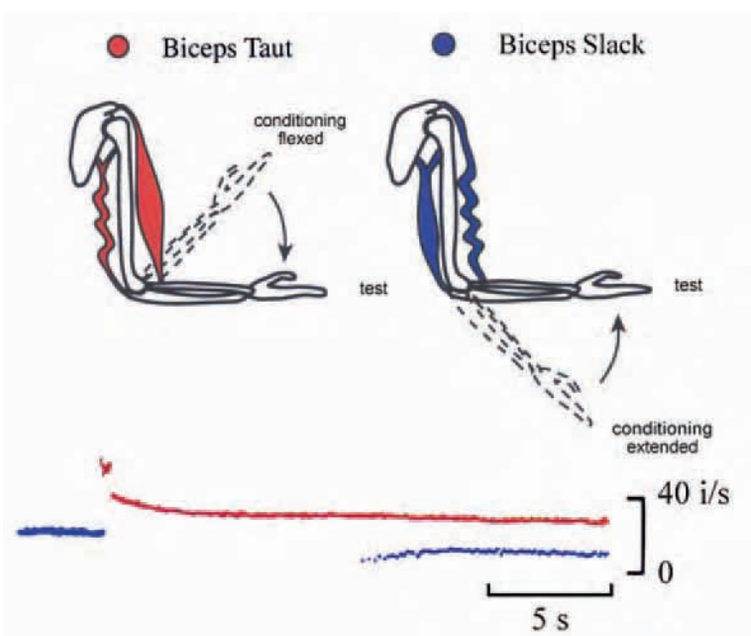

Figure 1. The technique of muscle conditioning. The two diagrams at the top show a human forearm with one flexor and one extensor muscle drawn in. On the left, the arm is held flexed (dashed lines) and the flexors are contracted (conditioning flexed). Once the arm has relaxed it is moved to an intermediate angle (test). This leaves biceps and its spindles in a 'taut' state. When the arm is held extended (dashed lines) and elbow extensors are contracted (conditioning extended), moving the arm to the intermediate angle (test) leads to development of 'slack' in biceps and its spindles. The lower diagram shows an instantaneous frequency display of the responses of a soleus spindle in the cat following conditioning of the muscle leaving the spindle taut (red) or slack (blue). Redrawn, in part, from Wood *et al.* (1996).

that by conditioning the muscle it is possible to alter spindle responsiveness without changing the length of the muscle. That, in turn, means subjects make conditioning-dependent errors in a forearm matching task (Gregory *et al.* 1988).

To explain how we use muscle conditioning to explore position sense I have drawn a simple diagram (Fig. 1). Contracting elbow flexors with the arm held flexed leads the intrafusal fibres in elbow flexor spindles to lie 'taut', generating strain on sensory endings and producing high levels of resting discharge in the spindles. When the relaxed arm is placed at an intermediate test angle, activity levels in flexors will continue to be high, in extensors they will be low. The subject interprets the high discharge levels as a muscle that is more stretched than it really is. It leads subjects to make matching errors in the direction of arm extension.

If now the contraction is repeated but with the arm held extended, during the subsequent movement to the test angle, flexor muscles and their spindles fall slack, leading to a low resting discharge (Fig. 1). By contrast, extensor spindle activity will be high. It means that after extension conditioning subjects perceive their forearms to be more flexed than they really are. By using the two forms of conditioning, total errors in position sense of 20º can be achieved, representing about a quarter of the full range of elbow movements available to the subject under the conditions of our experiment. So the effects of conditioning are considerable.

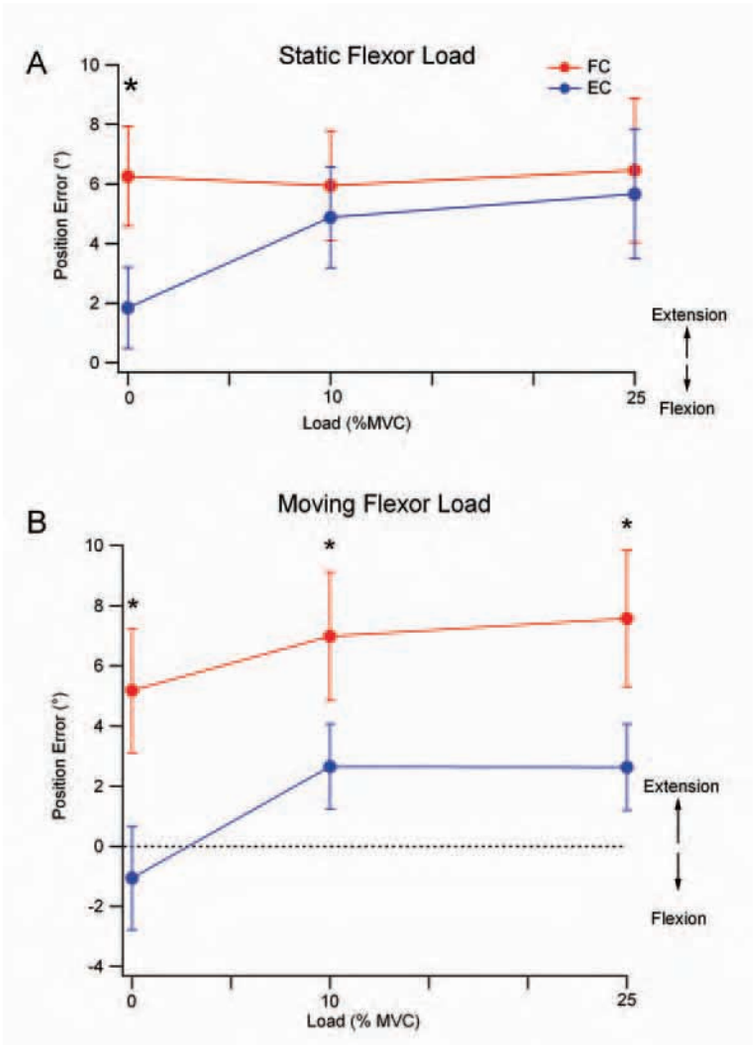

Figure 2. Position sense in the horizontal plane. Panel *A* shows data when subjects were required to support a load at the test angle. In panel *B*, following muscle conditioning the subject moved the loaded arm to the test angle. Traces in red, means (± SEM) for nine3 subjects following flexion conditioning (FC), traces in blue, values after extension conditioning (EC).
Position errors have been calculated as the angular difference between reference and indicator arms. Positive errors, placement of the indicator arm in the direction of extension relative to the reference, negative errors placement in the direction of flexion. Dashed line, zero error. Values are shown for the unloaded reference arm, when it was supporting 10% MVC (maximum voluntary contraction) and when it was supporting 25% MVC. Asterisks indicate significant differences ($p < 0.05$) between errors from the two forms of conditioning. Redrawn from Ansems *et al.* (2006).

The usefulness of the conditioning method is that is provides evidence for a role for muscle spindles in position sense that is quite different from the effects of muscle vibration. It is unlikely that other potential contributors to position sense, joint receptors and skin stretch receptors, will show muscle conditioning-dependent effects.

The question that has consumed me in recent times is how does position sense work when limb muscles are contracting? For the forearms, how do we know where our arms are when we support them against gravity, or when they are bearing a load? The important consideration here is that whenever we carry out a voluntary contraction to support our limbs the intrafusal fibres of muscle spindles are contracted as well. This is called co-activation (Vallbo, 1971). It means that as soon as limb muscles become active, the spindle signal fed back to the brain from those muscles increases dramatically. Now we face a new problem. How is the brain able to distinguish between spindle impulses generated as a result of muscle length changes from impulses generated from intrafusal contraction? It is really that question which fascinates me.

Rather than go through the various hypotheses that have been put forward in an attempt to solve this problem, I would like to describe some recent observations from our laboratory relevant to the topic (Ansems *et al.* 2006).

We chose to carry out the measurements of position sense about the elbow joint in the horizontal plane. The reason for doing this was that we did not want our observations to be

complicated by the effects of gravity. The arm was supported by a cradle that rotated about a pivot point coaxial with the elbow joint. Movement of the relaxed arm was almost effortless. Position of one arm, set by the experimenter, was matched by the other, moved by the subject. In addition, by means of a series of pulleys arm muscles could be made to support a load, or to move it.

The first thing we found was that when elbow muscles began to contract to support a load, the conditioning effects disappeared. They don't disappear immediately at contraction threshold, but become progressively smaller as the contraction grows until, typically with a strength of a quarter of maximum for elbow flexors, they are no longer significant. For a group of subjects, position errors of 4.5º from muscle conditioning in the relaxed muscle reduced to 0.8º at 25% MVC (maximum voluntary contraction, Fig. 2*A*).

We explain this result by proposing that where muscles and their spindles were slackened by conditioning (conditioning extended for elbow flexors in Fig. 1), the fusimotor activity accompanying a contraction leads to removal of the slack and to sensitisation of spindles. Therefore during a contraction the errors from flexion and extension conditioning converge towards the flexion conditioned state, where spindles are sensitised.

So the distribution of position errors at the forearm during loading supports the ideas that during a voluntary contraction the fusimotor and skeletomotor systems are co-activated. What, perhaps, is a little unexpected is that co-activation is distributed over about a quarter of the muscle's working range.

None of this helps us, of course, in understanding how position sense works during load bearing. What we considered to be a clue was that when flexor spindles were in their sensitised state (conditioned flexed, Fig. 1), loading flexor muscles did not introduce additional position errors.

During load bearing, the fusimotor activity would be expected to produce a large increase in spindle discharges, yet position errors remained unchanged. Nor was there any evidence of subjects becoming more erratic in their matching ability. Standard errors of the mean remained about the same (red trace, Fig. 2*A*). So whatever theory is used to explain position sense during load bearing, it must take such a result into account.

There is one more clue to add to the puzzle. When a passive muscle is vibrated, as mentioned earlier, it leads to illusions of limb movement and changed position. We measured the position error from vibration of the passive muscle and compared it with errors during vibration of a contracting muscle. Interestingly the position errors from vibration were gone at 25% MVC (Ansems *et al.* 2006). We believe that fusimotor-activated spindles are still vibration sensitive (Brown *et al.* 1967) but they do not seem to generate any illusions. Is it possible that fusimotor-activated spindles no longer have access to consciousness?

Finally, we tried a slightly different approach. Following muscle conditioning, the subject was required to move a load from the conditioning position to the test angle. This time the difference in conditioning effects did not disappear on loading the arm (Fig. 2*B*). It was as though moving a load introduced an additional signal that produced errors which added to the errors from conditioning, particularly when the conditioning had sensitised spindles (red trace, Fig. 2*B*).

To conclude, we have made a number of observations on position sense at the forearm during contraction of elbow muscles. While the picture remains fragmentary, we have provided new directions for future experiments. We no longer believe that the sense of effort accompanying support of a load provides positional information in any simple way (Walsh *et al*. 2004).

Our current working hypothesis is that when we move a loaded arm the brain listens to the feedback during placement of the arm and compares it with feedback levels generated in the past from similar movements. This information is used in deciding where to place the other arm in a position matching task.

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The Babraham Institute co-ordinates new European infrastructure in proteomics

The Babraham Institute, Cambridge is the co-ordinating partner for a new European research infrastructure, 'ProteomeBinders', which aims to understand how the human genome functions by studying its proteins.

The project, funded through the European Commission's 6th Framework Programme, sets the stage for an open-access resource of binding molecules directed against the entire human proteome, the full set of over 100,000 proteins specified by the human genome.

Established with initial funding of €1.8M over 4 years, 'ProteomeBinders' is co-ordinated by Dr Mike Taussig, Head of Babraham's Technology Research Group and brings together 26 European partners from 12 countries, and two from the USA.

As one of the largest genome-scale projects in Europe, this resource will impact on healthcare, diagnostics, target discovery for drug intervention and therapeutics and will consequently deliver advantages to the research, medical and biotechnology communities.

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Thought to action: development of temporal signals from topographic maps


David Waitzman (left) and Jason Cromer

Maintaining the stability of the eye during vision and shifting the eye rapidly to view different locations are two of the major tasks of the oculomotor system. Different populations of neurons in the visual pathways become active depending on where light falls on the retina (a spatial code). In contrast, single motor neurons that drive the muscles of the eyes encode the amplitude of muscle contraction via the number of spikes in their burst and the speed of contraction by the rate at which spikes are emitted (a temporal code). To perform the task of repositioning the eye with a high degree of accuracy, the central nervous system must provide a rapid and accurate mechanism via which activity related to a sensory perception is translated into appropriate movements. In neuronal terms, this question can be rephrased into understanding how the activity of topographically arranged, spatially encoded neurons of the visual system is transformed into the time varying spike train of the motor neurons that is necessary to drive the eye muscles. This article summarizes recent data suggesting how the change from spatial to temporal coding occurs.

The superficial layers of the superior colliculus (SC) located in the dorsal portion of the midbrain receive direct retinal and visual cortical input and contain a topographic map of the contralateral field of vision comparable to that in the visual cortex (see Wurtz & Goldberg, 1989 for review). Below the superficial layers, neurons in the intermediate and deep layers of the SC are activated just before the occurrence of rapid eye movements that shift the fovea a specific amplitude and direction relative to its previous position. In analogy to the sensory receptive field of the visual system, the array of eye movements which activate a SC neuron describes a 'movement field' (Fig. 1*A*).This structural arrangement of a pure sensory region above and a 'movement associated layer' below sparked considerable interest and suggested an opportunity to explore the transformation of visual information into motor activity, a so-called spatial to temporal transformation or STT (Fig. 1*C*) (Sparks & Mays, 1990).

However, despite an exhaustive evaluation of the SC activity, the underlying nature of this transformation remains elusive. Indeed, most investigators agree that the discharge of neurons in the intermediate and deep layers of the SC encode the intended target of a saccade, but *do not* encode the metrics of the movement (i.e., neither the number of spikes nor the rate of discharge is related to movement amplitude or velocity) (Bergeron *et al.*

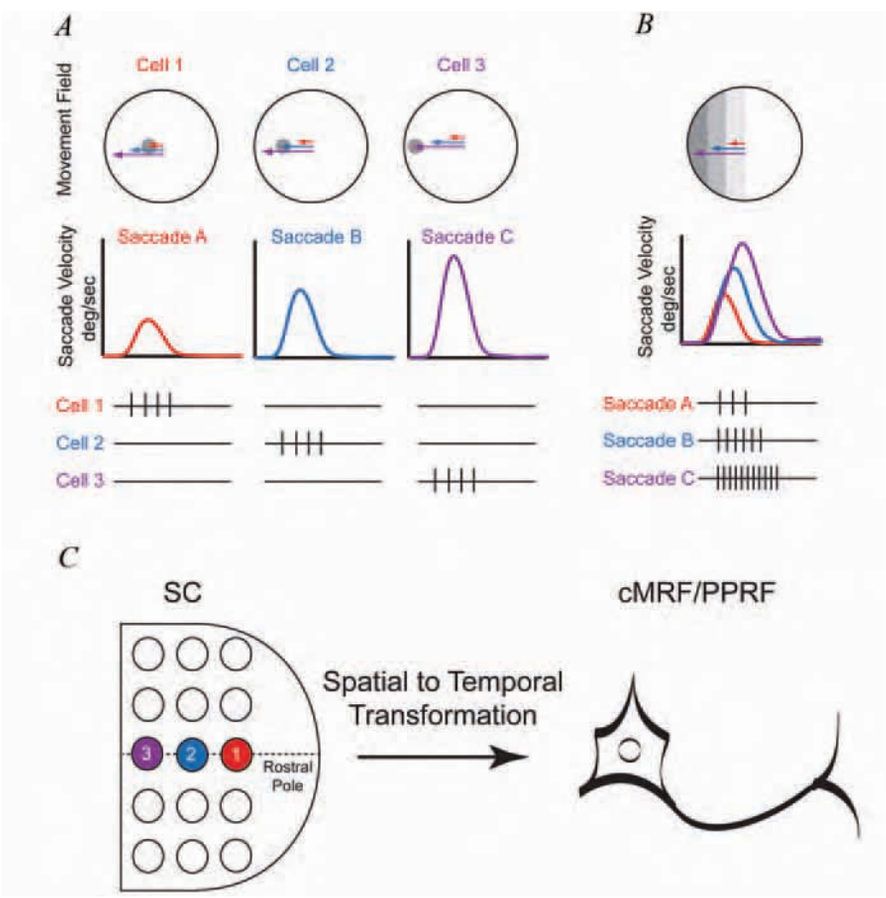

Figure 1. Schematic showing the elements of a sensory to motor transformation. *A* A series of superior colliculus (SC) cells positioned from rostral to caudal along the horizontal meridian of the SC have closed movement fields with response areas (grey color indicates the size of the movement field) for progressively larger amplitude saccades (cells 1, 2, and 3, see panel *C*). Small horizontal saccades would activate cell 1, medium amplitude saccades would activate cell 2, and large horizontal saccades would activate cell 3. Note that the discharge of each cell is the same regardless of amplitude (spike discharges shown below the eye velocity traces) and only occurs if the intended movement is into its movement field. *B* Single neurons in the cMRF and PPRF have activity that increases in duration with saccade amplitude and whose peak frequency increases with saccade velocity (compare the discharge of the single cell in this panel to the three cells associated with the same amplitude saccades in panel *A*). Both of these features are not evident in the discharge of neurons in the intermediate and deep layers of the superior colliculus (*A*). Thus, temporally coded neurons have movement fields which have no limit with respect to amplitude and encode the metrics of saccades in the timing and number of spikes in their bursts. *C* The SC is topographically arranged. The activity of a particular locus of SC neurons defines the intended amplitude of the saccade that will be generated. The rostral pole is to the right and the dashed line indicates the horizontal meridian. Neurons located further from the rostral pole have movement fields associated with larger movements. For example, the colored loci correspond to the location of cells (1-3) in panel *A*. From this population of closed movement field cells, the temporal activity of the downstream cMRF and PPRF neurons must be generated by a spatial to temporal transformation.

2003). Thus, one of the major questions in oculomotor control has been to understand how temporal signals like those of the neuron shown in Fig. 1*B* that encode the dynamics of saccadic eye movements are developed.

Location of temporally coded neurons

Temporal signals encoding eye movement dynamics are the end result of the STT. Over the last three decades a number of laboratories have searched for evidence of such signals in the structures targeted by neurons of the intermediate and deep layers of the SC (see Moschovakis *et al.* 1996 and Scudder *et al.* 2002 for reviews). Areas of particular interest are positioned downstream of the SC and include portions of the mesencephalic and pontine reticular formations (MRF and PPRF) and the nucleus reticularis tegmenti pontis (NRTP), the primary gateway to the cerebellum for the oculomotor system. These structures provide either direct or indirect access to abducens motor neurons.

The paramedian portion of the pontine reticular formation (PPRF) forms part of the direct pathway. The PPRF receives anatomically weighted, contralateral projections from the SC (Grantyn *et al.* 2002) and the axons of its burst neurons impinge directly upon abducens motoneurons (Fig. 1*C*, Fig. 2). The number of spikes in each burst of a PPRF neuron is monotonically related to the amplitude of each saccade while the discharge frequency of the PPRF burst neurons is directly related to the instantaneous velocity of the saccade (Fig. 1*B*) . The duration of the PPRF burst is tightly regulated by a group of inhibitory neurons located along the midline of the pons in the raphe interpositus (Buttner-Ennever *et al.* 1988). Since these neurons have a tonic level of activity and pause for saccades in all directions, they have been dubbed 'omnipause neurons' (OPNs) (Fig. 2).

The central Mesencephalic Reticular Formation (cMRF), located just lateral to the oculomotor nuclei and ventral to the superior colliculus (Horn, 2005), receives *ipsilateral* afferents from the SC and it forms reciprocal connections

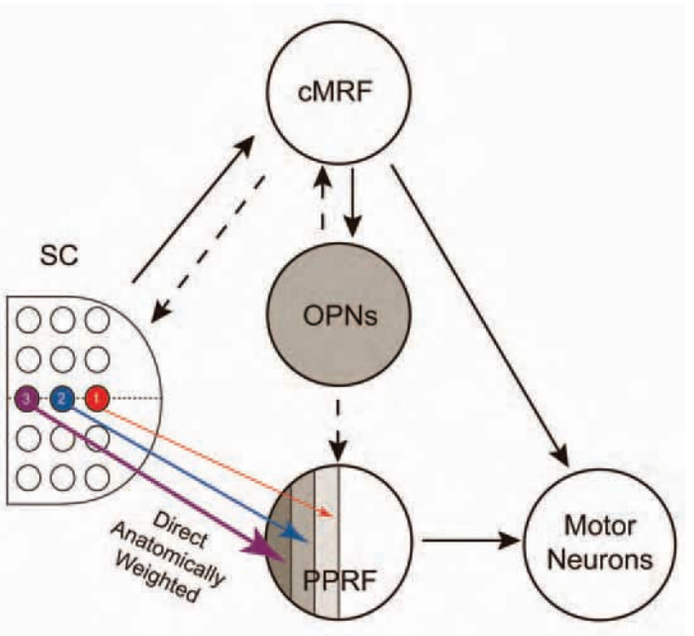

Figure 2. Schema for the sensorimotor transformation between the spatially coded superior colliculus and the temporally coded PPRF. The direct pathway uses anatomic weighting to generate an *estimate* of the ideal saccade trajectory. Indirect pathways refine the metrics of the movement. One potential indirect pathway is shown (SC → cMRF → Omnipause → PPRF), whereby recursive, excitatory loops between the SC and the cMRF and between the cMRF and the omnipause neurons can modulate the anatomic weight provided by the colliculus to the PPRF. Abbreviations: SC, superior colliculus; OPNs, omnipause neurons located in the raphe interpositus; cMRF, central mesencephalic reticular formation; PPRF, paramedian portion of the pontine reticular formation. Dashed arrows indicate inhibitory connections while solid lines depict excitatory connections.

with the SC and the omnipause neurons The majority of cMRF neurons provide a burst of spikes that are most closely associated with contralateral saccades. Recent recordings from cMRF neurons have demonstrated that the number of spikes and frequency of discharge in the saccade associated bursts are correlated with saccade amplitude and instantaneous velocity similar to the bursts in PPRF neurons (Fig. 1*B*) (Cromer & Waitzman, 2006). Indeed, many of the neurons had a monotonically increasing relationship between spike number and saccade amplitude and burst duration was closely correlated with saccade duration. While the correlations for cMRF burst neurons are generally weaker than those in the PPRF, nevertheless, these temporal signals could influence motor neurons via direct projections from the cMRF to the abducens nucleus (Ugolini *et al.* 2006) or via an indirect path mediated via reciprocal connections with the omnipause neurons (Fig. 2).

The spatial to temporal transformation

Despite the identification of temporally encoded neurons, the question remains as to how a topographically defined locus of activity in the superior colliculus that occurs approximately 40 ms in advance of saccades is molded into a burst of impulses related to saccade amplitude, duration, and instantaneous velocity that can activate extraocular motor neurons 20 to 25 ms later?

While neurons in the SC do not typically display relationships to saccade metrics, their discharge *duration* may reflect changes that occur in downstream structures (Goossens & Van Opstal, 2000; Soetedjo *et al.* 2002b). However, the close relationship between the discharge of cMRF and PPRF neurons to instantaneous eye velocity requires a physiological mechanism that can utilize the locus of SC activity, which is poorly associated with the metrics of the saccade, to generate the highly correlated time varying signals related to eye amplitude and velocity (Fig. 1*C*). While the density of projections between the SC and the PPRF likely contributes to the generation of these temporal signals (Fig. 2), it cannot be the only mechanism via which these tightly controlled signals are created.

A number of physiologic models have been postulated to explain how the STT occurs. One suggestion is that a series of SC neurons projecting onto neurons in the PPRF are sequentially activated at a particular rate to develop not only the correct spike number, but the time variation associated with velocity found in these target neurons (Munoz & Wurtz, 1995). However, physiological evidence for such a spread of activity across the primate SC has not been found (Keller & Edelman, 1994; Soetedjo *et al.* 2002a). An alternative idea suggests that the SC provides an idealistic drive and that the exact metrics of the pontine burst are shaped by cerebellar outflow that also impinges on the PPRF neurons (Quaia *et al.* 1999). This model shifts the idea of spreading activity away from the SC to the cerebellar vermis, for which again there is little physiological evidence (Robinson & Fuchs, 2001).

A different approach has posited that a recursive excitation loop between the cMRF and the SC could prolong the collicular outflow (Cromer & Waitzman, 2006). In this schema activation of a collicular locus would *trigger* excitation in this recursive pathway and possibly a similar loop between the cMRF and the omnipause neurons (Fig. 2). These recursive loops could generate a persistent burst whose number of spikes and duration corresponded with the desired saccade amplitude as long as a second signal appeared to appropriately shut down the loop thereby ending the saccade. The origin of this 'shut-down' signal is unclear, but could arise via a second indirect pathway that utilizes projections from the SC to the NRTP which projects in turn to the fastigial oculomotor region of the the cerebellar vermis whose cells are activated with saccade end (Ohtsuka & Noda, 1991; Fuchs *et al.* 1993; Quaia *et al.* 1999). While the exact mechanism for the STT remains an area of active research, generation of the burst in PPRF neurons that is tightly coupled to saccade dynamics probably occurs via modulation of the direct tecto-pontine projection (Fig. 2, direct pathway) by indirect pathways. This idea is attractive since it keeps most of the machinery necessary for developing and monitoring the time varying signals for saccades downstream from the SC. Moreover, this approach would permit topographically organized cortical regions such as the frontal eye fields access to the same eye movement generator utilized by the superior colliculus.

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Pearls from Society minutes

W D M Paton, who was Meetings Secretary in the early 1950s, produced minutes that captured the humour which permeated Meetings in those relaxed days before Teaching Quality Assessments, Research Assessment Exercises and other bureaucratic horrors. The Mill Hill Meeting in 1954 included discussion of the suggestion from R C Garry and J S Gillespie that the term 'orthosympathetic' be adopted as the twin for 'parasympathetic'. B Katz made an alternative suggestion: 'sympathetic' and 'unsympathetic'.

In the same minutes Paton mentioned the latest aids to audibility. He reported that 'Each speaker, when he reached the dias, was invested with electronic regalia, which amplified all the noises (intended and unintended) emanating from him and allowed the control engineer to produce some interesting effects.' On another occasion a Secretary recorded that 'Last year's Mayor's chair-type of microphone was this year replaced by a more fearsome model which gave the impression that the speakers were in the deadly embrace of a gigantic surrealist spider.'

The advent of PowerPoint has undermined The Society rule that no Communication should be read. Until relatively recently, reading was severely condemned since it makes for boring presentations and goes counter to the training in communication The Society seeks to provide.

The degree of disapproval engendered in one audience was recorded in the minutes of a Meeting in the 1950s. Reporting on a Communication about LSD, the Secretary said that the drug 'in an oral dose of a few micrograms induces in about 20 minutes certain mescalin effects such as distortion of the bodily image and loss of interest in the surrounding (*sic*). The latter of these actions was also produced even more rapidly in Members of The Society by the five or six authors who *read* their papers.

Culled by Ann Silver from Bynum WF (1976). A short history of The Physiological Society 1926-1976. *J Physiol* **263**.

Store-operated calcium entry in adult skeletal muscle fibres: the missing clue


Bruno Allard (left) and Vincent Jacquemond

Changes in cytoplasmic Ca^{2+} concentration are of ubiquitous importance to the function of living cells. A rise in cytoplasmic [Ca^{2+}] can occur from either Ca^{2+} entry through the plasma membrane or Ca^{2+} release from an intracellular store, mainly the endoplasmic reticulum. One obvious difference between the two mechanisms is that the store has a finite content and will, to some extent, get depleted upon substantial activation of a Ca^{2+} release process. In the past 20 years considerable evidence has been accumulated supporting the existence of a specific plasma membrane Ca^{2+} entry pathway meant to refill emptied (or partially emptied) Ca^{2+} stores. Although there is sparse indication that, in certain cell systems, a direct pathway between the extracellular medium and the lumen of the store could do the job, the most widely accepted view is that the way is through the cytoplasm. Then, store depletion-induced Ca^{2+} entry generates a cytoplasmic [Ca^{2+}] elevation, the role of which goes in fact well beyond replenishment of the store as it appears to be strongly relevant for various cell signalling processes. The study of 'store operated calcium entry' has become an extensive field of research, covered recently by a number of comprehensive reviews (see, for instance, Parekh & Putney, 2005).

The adult skeletal muscle fibre is a robust archetype of a cell relying on an intracellular Ca^{2+} store for its function: Ca^{2+} release from the sarcoplasmic reticulum (SR) is activated by membrane depolarization and generates the cytoplasmic [Ca^{2+}] elevation that triggers contraction, whereas Ca^{2+} entry through the plasma membrane is not relevant to this process (see Melzer *et al*. 1995). Actually even the most well known Ca^{2+} entry pathway in skeletal muscle (through the voltage-dependent slow Ca^{2+} channels) has no clear established function. Still, and although the store-operated Ca^{2+} entry concept is mostly popular in non-excitable cells, the possibility was there too, that SR Ca^{2+} depletion would trigger a specific Ca^{2+} influx through the plasma membrane of skeletal muscle fibres. This was supported by a series of experimental data by Kurebayashi & Ogawa (2001), showing in particular that the rate of Mn^{2+} entry into muscle fibres (measured by a fluorescence quenching approach) was increased when the SR was severely depleted. This study was an encouraging piece of work, prompting further analysis of the physiological properties of store-operated Ca^{2+} entry in muscle. The interest of this quest further gained in intensity when it was suggested that dysfunction of store-operated channels belonging to the TRPC (transient receptor potential canonical) family was responsible for an abnormal, potentially detrimental, influx of Ca^{2+} in dystrophin-deficient muscle (Vandebrouck *et al*. 2002). One could then put a name to an ion channel protein with an identified gating mechanism in relation to the dystrophic pathology. Interestingly, the unitary activity of the corresponding ion channel appeared well resolvable with the cell-attached patch-clamp technique and actually was very similar to a single channel activity previously shown to be particularly high in dystrophin-deficient cells by several groups (see Gillis, 1999). This is important because in many other instances, store-operated calcium entry was proven easier to reveal with fluorescent methods than with membrane current measurements. At that point we thought that a further in-depth characterization of the store dependent Ca^{2+} influx in control and dystrophin-deficient muscle fibres could bring precious information into the field. More specifically, we were very interested in the possibility of directly measuring the store-dependent membrane current under acute conditions of SR Ca^{2+} depletion, in an intact muscle fibre under voltage-clamp. This latter condition is of critical importance as membrane polarization is a non-avoidable parameter if one wishes to study the physiological properties of either trans-plasma membrane or trans-SR membrane Ca^{2+} fluxes in muscle cells, and thus *a fortiori* when studying a possible relationships between the two, as is the case for an SR-operated Ca^{2+} entry mechanism. Since voltage-clamp

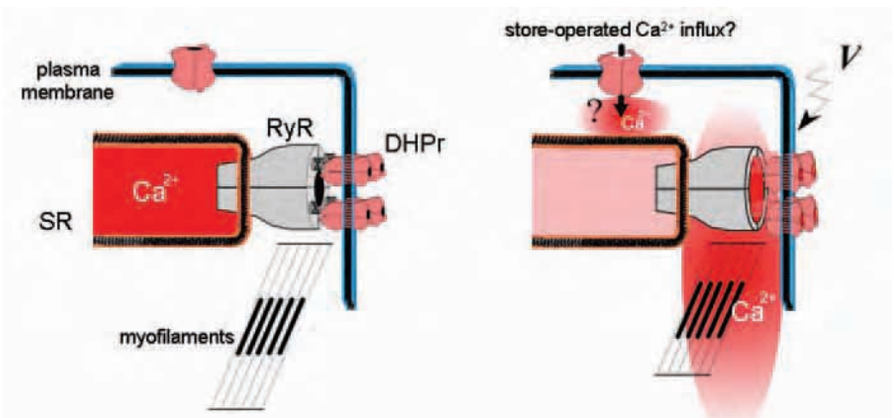

Figure 1. Simple scheme illustrating the possibility of a store-operated Ca^{2+} entry in skeletal muscle. Under physiological conditions, membrane depolarization triggers sarcoplasmic reticulum (SR) Ca^{2+} release through an interaction between the dihydropyridine receptors (DHPr) in the plasma/transverse-tubule membrane and the ryanodine receptor (RyR) in the junctional SR membrane; the resulting rise in cytoplasmic [Ca^{2+}] triggers contraction. Consecutive Ca^{2+} depletion in the SR would turn on a Ca^{2+} influx through the plasma membrane.

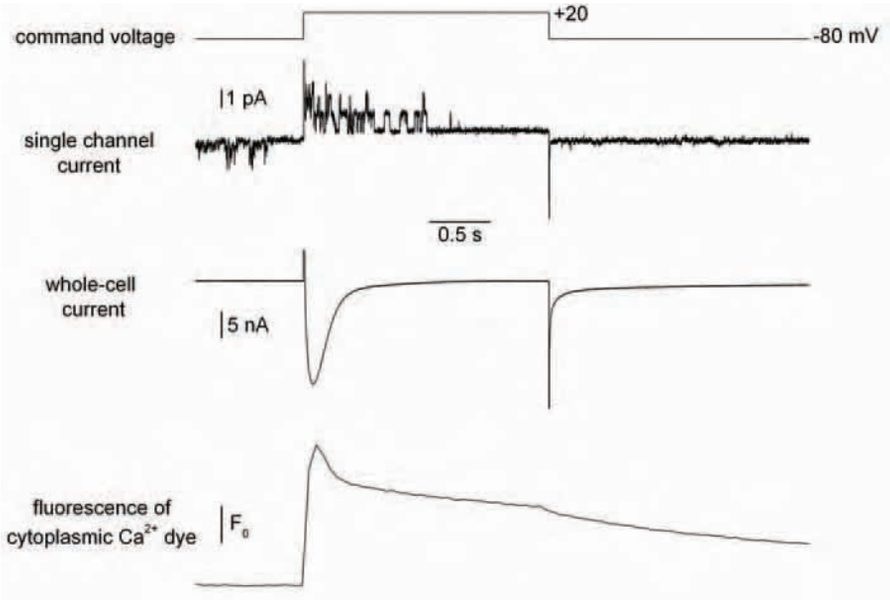

Figure 2. Illustrative examples of the different signals that were collected simultaneously from the same muscle fibre when looking for the store-operated Ca^{2+} current. The plasma membrane ion channel activity was followed at the unitary level with the cell-attached patch-clamp technique (single channel current) and at the macroscopic level (whole-cell current) with the silicone voltage-clamp technique. Records were taken while the fibre was depolarized by a 2 s-long depolarization from -80 to +20 mV. The change in intracellular Ca^{2+} concentration was followed from the fluorescence of fluo-3. The cell-attached pipette contained Tyrode and the external solution contained only calcium as permeant cation. The cell-attached patch-clamp record shows the activity of channels carrying inward current at -80 mV before the pulse and of the delayed rectifier K^+ channels during the pulse. The whole-cell current trace shows the slow inward calcium current that activates and inactivates during the depolarization.

had so far not been used in previous studies of store-operated Ca^{2+} entry in muscle fibres, we thought this may be a key to a wide, unexplored aspect of the problem. We worked things out trying to gather the best possible sets of experimental conditions so that we would not miss the store-operated Ca^{2+} current. This included, on the same muscle fibre, a combination of either two or three techniques: whole-cell voltage-clamp (allowing control of SR Ca^{2+} release and measurement of the total membrane current), cell-attached patch-clamp (for tracking the above-mentioned store-dependent-suspected unitary channel activity) and detection of the fluorescence of a calcium dye injected within the cytoplasm of the fibre. Well, despite our efforts, all this failed! We tested a vast array of experimental protocols and conditions aimed at depleting the SR such as repetitive large membrane depolarizations, use of SR Ca^{2+} uptake blocking agents or of SR Ca^{2+} releasing agents, but never detected any reproducible change in either unitary or whole-cell membrane current that would be consistent with a store-operated Ca^{2+} influx (Allard *et al*. 2006).

Now why is that? How could it be that the Ca^{2+} influx would not show up under these conditions, when SR Ca^{2+} depletion was assessed and membrane current measured at both the macroscopic and unitary levels? Why could not we detect any sign of an inward current? One could speculate that, for obscure reasons, SR content-dependent Ca^{2+} entry did not operate under this specific set of conditions. Conversely we tend to believe that assessing the existence of a store-depletion induced Ca^{2+} influx in a muscle fibre out of voltage control is quite hazardous. Another possibility would be to consider that the influx is too small to be detected as a current with electrical methods whereas it would be detectable with fluorescent quenching techniques. Still, then what would be the physiological relevance of this non-electrically detectable current when, for instance, we know that there is a clear well-detected Ca^{2+} entry through the voltage–dependent Ca^{2+} channels upon membrane depolarization, the role of which is unknown. This makes the physiological relevance of this putative store-operated Ca^{2+} entry very much questionable. There are several other detailed aspects of the problem as well that may be discussed but overall it seems that in the absence of new related experimental data the controversy will stand.

Acknowledgements

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Peripheral muscle fatigue from hyperoxia to moderate hypoxia – a carefully regulated variable?

Members of the John Rankin Laboratory of Pulmonary Medicine. From the left: David Pegelow, Markus Amann, Jerome Dempsey and Anthony Jacques.

How does the central nervous system (CNS) regulate athletic performance in different environmental conditions from below sea level exercise to exercise at moderate altitudes? What is the role of peripheral muscle 'fatigue' in endurance performance – is it a major determinant?

Fatigue is defined as the reduction in force/power generating capacity of the neuromuscular system that occurs during sustained exercise and is subclassified into a 'peripheral' and a 'central' element. It is generally agreed that much of the loss of force/power results from biochemical changes within the working muscle (i.e. peripheral fatigue) (Fig. 1*A*). However, the loss of force/power can also result from inadequate muscle activation – often, but not exclusively, in combination with failure of contractile mechanisms – resulting from a reduced motor drive by the CNS to the working muscle (i.e. central fatigue) (Fig. 1*B*). Several mechanisms which are not mutually exclusive have been suggested to underlie central fatigue (Gandevia, 2001). For example, afferent neural feedback mechanisms originating in various peripheral organs (Fig. 1*C*), including the working muscles (Fig. 1*D*) might affect brain cortical processes and the CNS might in turn modulate central motor output accordingly to ensure a specific level of organ system homeostasis and protect the organism from damage. Alternatively, exercise-induced changes in cerebral neurotransmitter activities (i.e. serotonin) (Fig. 1*E*) (Meeusen & De Meirleir, 1995) and/or the effects of various environmental/physiological conditions (e.g. heat stress or hypoxia) (Gandevia, 2001) (Fig. 1*F*), *per se,* might affect the control of motor activity in the brain and thus whole body exercise performance, independent of any peripheral sensory feedback mechanism.

Peripheral muscle fatigue can be assessed objectively and reproducibly using, for example, supra-maximal motor nerve stimulation. However, the evaluation of central motor output (and central fatigue) during dynamic whole body exercise, must rely on more indirect measures of the muscle electromyogram, which are prone to artifacts.

We have previously demonstrated a highly sensitive effect of arterial oxygen content (C_aO_2) on the rate of development of peripheral muscle fatigue during dynamic whole body exercise (Amann *et al.* 2006a) (Fig. 1*G*). Even relatively small reductions in hemoglobin saturation (S_aO_2) below resting levels (as occurs during heavy sustained exercise at sea level or at moderate altitudes (-6 to -10% S_aO_2)) exaggerated the rate of development of peripheral muscle fatigue, whereas increases of C_aO_2 significantly attenuated this rate. In a subsequent investigation (Amann *et al.* 2006b) we varied levels of C_aO_2 via changes in the inspired O_2 fraction (F_IO_2 0.15 to 1.0) to manipulate the rate of fatigue accumulation during bicycle ergometer time trial performance tests in which trained athletes attempt to cover 5 km in the shortest time possible. This type of exercise performance test mimics real-life competitions wherein the performer must make second by second decisions concerning the magnitude of his power output. Average central motor drive, estimated by integrative electromyography of the locomotor muscles, was strongest during the high C_aO_2 time trial (F_IO_2 1.0) and weakest during the condition of reduced C_aO_2 (F_IO_2 0.15). Accordingly, the highest average power output and the best exercise performance (i.e. shortest time to finish the time trial) was achieved in the high C_aO_2 trial and vice versa. The striking finding of this study was that, despite marked differences in central motor output, power output and exercise performance time, the level of peripheral muscle fatigue induced by the various time trials was almost identical (Amann *et al.* 2006a). Together, these data indicate that as the level of arterial oxygenation was altered during exercise the CNS received sensory input which was used to up- or down-regulate central motor drive to adjust for the respective rates of peripheral muscle fatigue accumulation. Therefore, an 'excessive' development of end-exercise peripheral muscle fatigue beyond a critical threshold or 'sensory tolerance limit' (Gandevia, 2001) was prevented. We then tested (and confirmed) this hypothesis in the same subjects using a high intensity constant load exercise test to exhaustion at varying F_IO_2 (Amann *et al.* 2006a; Romer *et al.* 2006).

How did the CNS know how to regulate motor drive and match contractile activity to the functional capacity – which was determined by C_aO_2? How might C_aO_2-dependent effects on the rate of development of peripheral muscle fatigue be 'sensed' and in turn impact central motor output? In other words, what provides

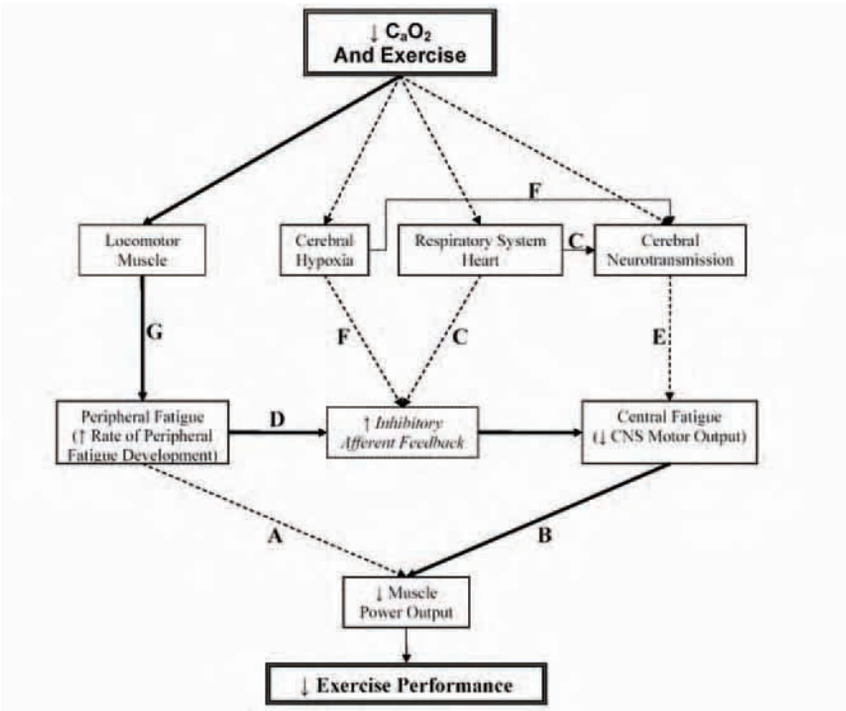

Figure 1. Hypothetical scheme linking a reduction in arterial O_2 content (i.e., acute exposure to moderate altitude) and exercise performance via its effects on fatigue. The solid lines graphically illustrate our proposed hypothesis. The dashed lines indicate other potential factors capable of affecting central motor output and exercise performance. Alterations in arterial O_2 content (C_aO_2) occur throughout the organism and affect various organ systems. Consequently, various organs might affect exercise performance via inhibitory feedback mechanisms controlling central motor output. Based on our measures of peripheral quadriceps fatigue and our estimates of central motor output (from quadriceps EMG), we propose that peripheral muscle fatigue is carefully regulated via modulations of CNS motor output to ensure muscle homeostasis during exercise from hyperoxia to moderate hypoxia. The relative importance of peripheral fatigue might diminish at more severe levels of hypoxemia and cerebral hypoxia might gain in relative influence on central motor output and the termination of exercise.

feedback to the working athlete allowing him to exercise close to his highest endurable rate of fatigue development without significantly exceeding it which would result in premature 'excessive' peripheral fatigue and jeopardize his maximal performance? We propose that metabolite accumulation (e.g. inorganic phosphate) whose rate of accumulation in contracting muscle is C_aO_2 dependent (Hogan *et al.* 1999) activates sensory nerve endings which project the rate of fatigue accumulation in the peripheral muscle to higher areas of the CNS (Taylor *et al.* 2000). Based on this afferent feedback the CNS will modulate central motor drive to optimize exercise performance while concurrently ensuring locomotor muscle homeostasis. The data point to the rate of peripheral muscle fatigue development as an important determinant of central motor drive and of exercise performance. Thus, the classical view which emphasizes the direct effect of peripheral fatigue on contractile performance is now extended by showing a connection between peripheral locomotor muscle fatigue and central motor output during whole body exercise.

It is important to emphasize that the rate of peripheral fatigue accumulation is certainly not the only potential source of inhibitory influences on central motor output and thus exercise performance. Significant influences of, for example, cerebral hypoxia on central drive have been indirectly implicated in several investigations. Based on these reports, we predict that the relative influence of our proposed feedback effect from fatiguing muscle on central motor output (Fig. 1*A*) will diminish as C_aO_2 is reduced below normoxic levels (i.e. exposure to higher and higher altitudes) and CNS hypoxia, per se, gradually increases its inhibitory influence (see Fig. 1*F*). Furthermore, there are surely systemic sources of inhibitory feedback – other than from fatiguing limb locomotor muscles. For example, in situations where expiratory flow limitation and lung hyperinflation occur during sustained exercise (highly trained subjects at maximum exercise, fit elderly and COPD patients), excessive respiratory muscle work or respiratory muscle fatigue are also likely to occur. In turn, reflex-induced supra-spinal sensory feedback occurs which will not only intensify cortical perceptions of effort but may also influence blood flow and O_2 transport to exercising limbs thereby exacerbating limb fatigue (Fig. 1*H*). We are currently investigating the relative influence of hypoxemia severity and respiratory muscle work on central and peripheral fatigue during exercise in health and in COPD patients.

In conclusion we need to emphasize that the physiologic determinants of central and peripheral fatigue and exercise performance are highly complex and controversial and certainly situation- and subject-dependant. Our correlative findings in healthy humans have provided only a first indication – albeit we believe a strong one – that exercise-induced peripheral muscle fatigue is likely to play a significant role in this process under many circumstances in health and in certain disease states.

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Going with the flow: just say NO to oxygen radicals

Endothelial cells are permanently exposed to shear stress by the flowing blood. Shear stress increases the endothelial formation of nitric oxide. But what happens to oxygen radicals during flow? Henning Morawietz and colleagues analyzed the flow-dependent regulation of the NADPH oxidase as a major source of endothelial oxidative stress

We all know the good advice of our physician to exercise on a regular basis. From the physiological point of view, a major beneficial effect of this everyday challenge could be an increase in blood flow. As the inner layer of our blood vessels, the endothelial cells are permanently exposed to shear stress throughout their lifetime. A well-known beneficial effect of increased shear stress is the augmented endothelial formation of nitric oxide (NO). NO does not only mediate endothelium-dependent vasodilation, but also anti-inflammatory and anti-thrombotic processes (Landmesser *et al*. 2004). Therefore, formation of NO by the endothelial NO synthase (eNOS) is a critical determinant of endothelial function. The NO availability can be limited by enhanced formation of reactive oxygen species like superoxide anions ($\cdot O_2^-$) (Bachschmid *et al*. 2005). NO and $\cdot O_2^-$ can form peroxynitrite in a very rapid reaction, thus reducing the available NO. An increased formation of reactive oxygen species has been considered as a major determinant of endothelial dysfunction (Harrison *et al*. 2003). Another detrimental effect of vascular oxidative stress is the increased oxidative modification of

Henning Morawietz

low-density lipoprotein thus promoting foam cell formation and atherosclerosis.

While several studies have addressed the impact of shear stress on NO formation, much less is known about the impact of shear stress on endothelial formation of reactive oxygen species. Our lab established a cone-and-plate viscometer as an experimental model to simulate different levels of shear stress on cultured endothelial cells more than 10 years ago (Fig. 1). Because the NADPH oxidase has been identified as a major source of reactive oxygen species like $\cdot O_2^-$ in human endothelial cells (Rueckschloss *et al*. 2003), in a recent study we analyzed the impact of laminar shear stress on $\cdot O_2^-$ formation and NAD(P)H oxidase subunit expression in human endothelial cells (Duerrschmidt *et al*. 2006). Short-term application of shear stress transiently induced $\cdot O_2^-$ formation in human endothelial cells. This was inhibited by the NAD(P)H oxidase-specific inhibitor gp91ds-*tat*, but NAD(P)H oxidase subunit expression was unchanged. In contrast, long-term arterial laminar shear stress downregulated $\cdot O_2^-$ formation, mRNA and protein expression of NAD(P)H oxidase subunits Nox2/gp91^{phox} and p47^{phox}. In parallel, endothelial NO formation and eNOS, but not Cu/Zn superoxide dismutase expression was increased. Interestingly, downregulation of $\cdot O_2^-$ formation, gp91^{phox} and p47^{phox} expression by long-term laminar shear stress was blocked by eNOS inhibition. Furthermore, an NO donor downregulates $\cdot O_2^-$ formation, gp91^{phox} and p47^{phox} expression in static endothelial cells. Our data suggest a transient activation of $\cdot O_2^-$ formation by short-term shear stress, followed by a downregulation of endothelial NAD(P)H oxidase in response to long-term laminar shear stress. NO-mediated downregulation by shear stress preferentially affects the gp91^{phox}/p47^{phox}-containing NAD(P)H oxidase complex. This novel mechanism might be involved in the shear stress-dependent regulation of the endothelial NO/$\cdot O_2^-$ balance (Fig. 2). An increased NO and decreased $\cdot O_2^-$ formation could also contribute to the vasoprotective potential of physiological levels of laminar shear stress. This would further support an intact and healthy endothelial function.

How can this be translated into cardiovascular physiology and pathophysiology? Short-term and long-term endothelial NO formation by shear stress can involve different mechanisms. While the first phase mainly represents a functional

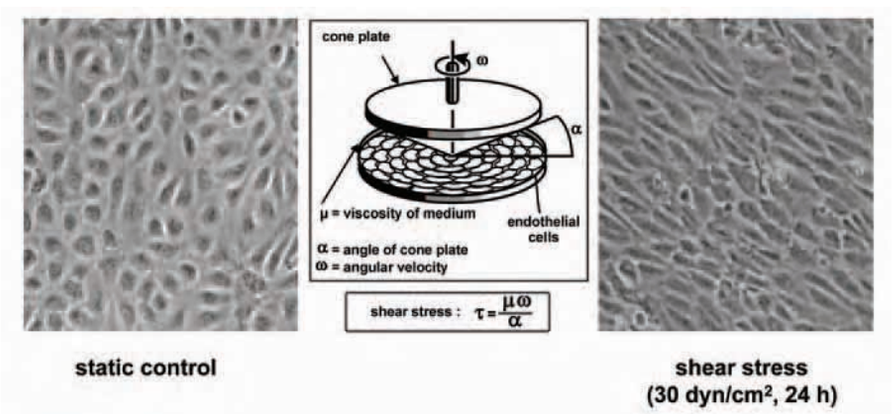

Figure 1. Application of shear stress to endothelial cells using a cone-and-plate viscometer. Human endothelial cells can be cultured under static conditions or exposed to shear stress using a cone-and-plate viscometer. The apparatus consists of a cone with an angle of 0.5° rotating on top of a cell culture dish. The degree of shear stress τ depends on the viscosity of the medium μ, the angular velocity ω, and the angle of the cone α. Long-term application of laminar shear stress (24 h, 30 dyne cm^{-2}) results in elongation of endothelial cells in the direction of flow.

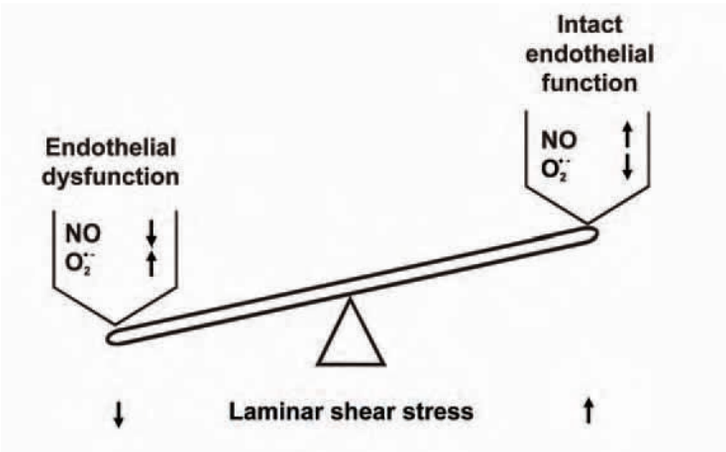

Figure 2. Laminar flow can regulate the endothelial NO/$\cdot O_2^-$ balance and endothelial function.

activation of eNOS, the second phase is accompanied by an upregulation of eNOS expression (Fleming & Busse, 2003). Similarly, short-term shear stress seems to activate NADPH oxidase activity. In contrast, long-term application of laminar shear stress downregulates $\cdot O_2^-$ formation and NADPH oxidase subunit expression. This makes physiological sense because both processes improve the vascular NO availability in response to increased laminar flow. Interestingly, NO even seems to be involved in the downregulation of oxidative stress by long-term laminar flow. This is not just a simple scavenging of $\cdot O_2^-$ by NO, because transcriptional downregulation of NADPH oxidase subunit expression by long-term laminar shear stress involves an NO-dependent pathway as well. Which NO-dependent transcription factors are involved in this process is currently not known.

Coming back to the initial advice of our physician, should we also exercise to balance our NO/$\cdot O_2^-$ ratio? The answer is definitely yes. Experimental studies in flow-adapted coronary arterioles and aorta support this concept. Increased blood flow in mice subjected to voluntary training reduces vascular $\cdot O_2^-$ release and NADPH oxidase subunit expression as well (Laufs *et al.* 2005). Finally, chronic exercise training of patients with coronary artery disease increases flow, decreases generation of reactive oxygen species and expression of $gp91^{phox}$ in internal mammary arteries, and improves endothelial function (Adams *et al.* 2005).

The bad news for all couch potatoes: the beneficial effects of exercise are only transient. We have to move on.

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Human Physiology

BIOS Instant Notes

By Daniel McLaughlin, Jonathan Stamford & David White

2006, Taylor & Francis. £18.99.

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This book does exactly what it sets out to do; it distils the richness and complexity of physiology down to the essentials. The question remains: is this a good thing or a bad thing? The publisher's claim that the book explains fundamental concepts and major physiological systems 'without overloading the reader with information' speaks for itself. The book should not be mistaken for a full textbook, despite its 460 pages; rather it should be viewed as a revision aid, which would act as a prompt for the reader who has access to that extra information, or as a complement to extended texts which treat the topics in more detail.

The difficult task of identifying core information is tackled admirably by the authors. The text is organised in a traditional, linear format. The material is presented using a cellular and systems-based approach with 13 sections, divided into 85 bite-sized topics. Specific topics are found easily using the table of contents, which is important for a revision text. 'Key notes' are contained in a box at the start of each topic and provide a summary of the information on that topic; the information is equivalent to the minimum 'take home' message from a lecture on the topic. Signposts to other 'related topics' at the end of the key notes acknowledge the integrated nature of the subject. The book also has a good index and a useful list of common abbreviations and acronyms, although the suggestions for further reading appear at the end of the book rather than at the end of a section.

The didactic presentation is in contrast to the interactive, multimedia style of most recent publications, and the lack of colour is also conspicuous. The diagrams are clear and concise, however, so the basic black and white presentation is to its advantage; the minimal style of the line diagrams should make it easy for students to reproduce them under exam conditions.

This book is aimed at students studying physiology as the foundation for degrees in the biomedical sciences or in the early stages of medicine; however, students with a primary focus on physiology would require a more extensive textbook. The optimist in me hopes that all students would demand more than this book has to offer; the cynic in me realises that many students may neither want, nor even need, more than this.

Sarah Hall

My first CONference

Recent letters in *Physiology News* (**64**, 22) brought back vividly the memories of the first conference I attended! Tired after an overnight journey, five of us were crammed into a room meant for three at the guest house. After a quick wash we hurried to the venue for the free breakfast that went along the inauguration. Festoons and banners and young volunteers with badges, greeted us. To my surprise I found policemen holding back the delegates from rushing to the tables, as the chief guest has

not yet arrived. The Minister who could reach the venue only half an hour later, looked confused about the distinction between physiologists and physicians and exhorted us to serve the rural poor! After the registration and a heavy breakfast, I marched to the venue armed with the gift bag containing all the papers and some thrills like a packet of Pan Masala (now banned). The venue was full of people from all walks of life – press with cameras and notepads, khaki-clad politicians who followed the Minister, defence personnel boldly displaying their decorations and, of course, physiologists. Included in the morning session were workshops on yoga and medical education. While contemplating which to attend, I noticed an elderly, sage-looking gentleman with a greying beard and turban approaching me, and asked for his suggestions. With a smile he replied that it all depended on whether I was a meditator (philosophically oriented, statistically disinclined) or a meducator (lab detesting, tongue twisting). Being neither, I chose to attend both, slipping in and out. In the first workshop I heard the benefits of breathing through the left nostril and of energy moving up from one chakra to the other, starting from the sacral spinal cord and ascending all the way to the cerebral cortex! The second workshop debated the acceptance of MCQs by medical students who pursued their high school education in native tongues. Excellent tea served after the workshops prepared me for the next session. I noted with dismay that the entire day was dedicated to the presentation of papers dealing with hypothalamus or hypoxia! Puzzled, I approached the sage for explanation. He said the day belonged to the capitalists (physiologists from Delhi who arrived on the morning flight). They followed two different paths of enlightenment – Anand Marg and Autar Marg. These two great schools of physiologists occupying their bastions in the new and old quarters of the city waged a war which often went beyond the realm of academics.

The evening meal was delicious with an assortment of choice local foods. I could meet and introduce myself to many senior physiologists(balding pates, protuberant bellies and the fluid levels in their glasses being the indicators).

Next day the attendance dwindled by half. Obviously the Delhi crowd had caught the night flight. As I was early, I found time to meet the sage. This time he asked me whether I belonged to any Navratnas (a term applied to well funded, star studded institutes of research, established by the government). The day belonged to them the sage informed me, and gently reminded me of a free tour of beaches arranged for the late afternoon. Some of the papers were quite interesting, the beaches far more.

Further decline in numbers was evident on the last day but new banners of drug companies appeared on the scene and the papers on pharmacology were due. I confessed to the sage that I felt a bit odd at the presence of politicians and pharmacologists. 'We need them', the sage said. 'The conference hall was given free of charge and the dinner where you ate chicken xacuti with relish was hosted by a pharmaceutical company'.

Since the few remaining delegates were in a hurry to catch trains, only a few papers were presented by physiologists like me. According to the sage they may be called 'generalists' spending a life time demonstrating simple muscle curves on smoked drums to mediocre medical students!

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PS More than three decades have gone by and I have attained a fairly senior level. Although I did not learn much physiology at my first conference, the contacts I made proved extremely useful. With their help I managed some small scale research. From smoked drums many labs moved to physiographs and some could obtain data acquisition systems. I still enjoy attending conferences and am encouraged to note the increasing participation of young people and the freshness in their approach. For with them lies the future of physiology in this country!

Fools rush in

J L Linzell, who did pioneering work on lactation using surgically prepared goats, once defined a physiologist as someone who chopped rubber tubing into short lengths that couldn't be re-used in any other experiment. Another essential for many experiments in systems physiology was Plasticine. This was ideal for anchoring the tubing, and for propping up glass connectors, taps, etc.

In 1952 I spent part of the summer vac working in Edinburgh with Catherine Hebb. This coincided with a Meeting of the British Pharmacological Society at which we demonstrated a perfused heart-lung preparation. I was standing beside the sealed perfusion chamber – a set-up that required many, many bits of tubing, all with their attendant Plasticine (which happened to be dark purple). One rather distinguished-looking man pointed through the lid at the lungs and said disparagingly 'Huh! Very cyanosed'. I unhesitatingly replied 'But that's Plasticine.' This was greeted with glee by the surrounding audience – the complainant was an eminent Member of both Societies.

Ann Silver

Tim Bliss and LTP

On 22 September they travelled from far and wide to pay homage to the man, his three letter acronym and more. Timothy Vivian Pelham Bliss, or Tim, is to retire after over 40 years service to the field of neuroscience. Organized with support from The Physiological Society and the British Neuroscience Association (BNA) to celebrate Tim's career, the symposium and following party were a delight.

Tim's pre-eminence among the international neuroscience community reflects his seminal description of the phenomenon of long term potentiation (LTP). However, the assembled hoards, the breadth of contribution from attendees encompassing cleaning staff, former artist in residence and a veritable collective noun of research scientists reflects affection and esteem that goes beyond just the key scientific contribution. Indeed, the ambience and spirit of the meeting truly reflected the contribution of one of the most British of neuroscientists.

His description of LTP (we assume it naturally exists so will not argue for its discovery) provides an experimental model of a long- lasting synaptic plasticity that has captured the imagination and we may yet see the day when such synaptic plasticity is proven to be the very basis of memory. The phenomenon, which has its roots in two seminal papers published over 30 years ago in *The Journal of Physiology*, the first with Terje Lømo and the second with Tony Gardner-Medwin, both of whom happily were present at the celebration, and arose out of Tim's early nomadic journey into the cortical substrates of learning. Yes – it appears he was looking for something akin to what he found! This settled him to his task and he became a staff member in the Neurophysiology Division at the National Institute for Medical Research (NIMR) in Mill Hill. Safely ensconced in his permanent home LTP became a driving force for many experiments conducted by Tim and co-workers. The research effort has also extended into the wider community in behavioural, systems, cellular and molecular neuroscience. Perhaps most impressive, even to those who have not been bitten by the LTP bug, is the way in which LTP has been at the heart of numerous research efforts and careers that have tried to integrate investigation across distinct organizational levels of the nervous system. It is through collaboration and the direct effort of his own lab that Tim's efforts have continued to shape the field and this sentiment was broadly reflected in the contributions made to his retirement symposium.

The event took place at Tim's current great passion, the aforementioned NIMR, and was centred on a symposium at which collaborators and friends each gave some perspectives on their current work and how their personal interactions with Tim over the years have affected some of their research. John O' Keefe (University College London) set the standard in describing the role of CaMKII in refining place fields in the hippocampus while simultaneously regaling us with tales of two seafarers. In this vein, the photographic evidence suggested that, despite his nautical heritage, Tim did well to discover his liking for synaptic plasticity and, as keenly scored by John O'Keefe, his penchant for bright shirts and outrageous socks.

Before we could 'slap him in irons' O'Keefe left the stage to Graham Collingridge (University of Bristol) who went on to give us two distinct lessons in metrics. The first involved highlighting the outrageously successful LTP review he had co-authored with Tim in 1993 and the incredible number of citations that this article had received. Based on citations alone it might well be screening soon as a classic adaptation in the BBC's Sunday Night drama spot. In the second, Graham described the distinct role that sub-types of the NMDA receptor play in particular forms of synaptic scaling, based on his and collaborators' work in Bristol.

Graham was followed by the meeting's furthest-travelled attendee – Cliff Abraham (University of Otago, New Zealand). Cliff has been a regular visitor to NIMR and a long-standing contributor to the debate about the existence and role of LTD in the mature nervous system. Cliff has pondered why plasticity can be so variable in slice and *in vivo* preparations and highlighted, with the support of mathematical modelling, why tonic activity or its loss in the slice may confound studies of LTD. Indeed, the supporting photographic homage to Tim on trips to the southern hemisphere will likely lead to a long queue for sabbatical leave to New Zealand.

After Cliff we left the hippocampus and delved into a world of pain as viewed by Steve Hunt (UCL). Steve touched on the existence of LTP among several other plasticity paradigms that might sub-serve a role in pain transmission in the spinal cord. Despite his long-standing collaboration with Tim, it was not clear who introduced who to whom.

Above: Tim Bliss at the meeting. Right: John Garthwaite, Graham Collingridge and John O'Keefe.

Nevertheless, Steve highlighted the contribution their collaboration had made in pointing towards the role of gene transcription in LTP. Steve reminded us of the charm that was and is Bliss before the pain of hunger kicked in. Participants retired to the pavilion for lunch.

Above: Tim Bliss adds his own words before stepping into retirement. Below: Serge Laroche

The post lunch session opened with Serge Laroche (Universitė Paris Sud, Orsay) taking guard and hitting us with insights into the role of transcription factors in LTP and, by experimental extension, memory and learning. Serge built up from here and highlighted that, at the time of the silver anniversary of his collaboration with Tim, there was plenty of scope to investigate how neuronal remodelling and neurogenesis supports brain plasticity.

Our next speaker, Marina Lynch (Trinity College, Dublin), informed us that she had required all her convent training to dodge questions about Saint Paul during the interview she had been subjected to on applying for a post-doctoral position at NIMR. In true 'Bliss'-style, the interview, and thus the selection of Marina as co-worker, had not actually been conducted by Tim. His views on Saint Paul remain unknown. Nevertheless, Marina assured us that she had been delighted with her time with Tim and she illuminated how her investigations of a potential role of arachadonic acid in LTP had led to her current focus on neuro-inflammation in the aged brain. Like many, Marina has successfully used hippocampal LTP as a robust assay of synaptic transmission and scores perturbation in its induction and maintenance as a measure of dysfunction. Despite Marina's self-deprecation about her own work it was clear to the audience that it is in the arena of addiction, stress and neurodegenerative biology that LTP will continue to feature in the future.

Post-Marina we were schooled in the optical imaging of synaptic transmission from a host of Tim's collaborators and one-time co-workers. These talks focused on the development and use of optical methods to decipher the cellular basis of LTP. The first of these was from Alan Fine (NIMR/Dalhousie University) who detailed how live and sequential imaging of neuronal structure and function could be used to re-open the long standing debate over the presynaptic component to the expression of LTP, and the degree to which structural re-organisation contributes to synaptic plasticity. Alan's talk also reminded us of Tim's long affiliation with Canada and its universities, having gained his PhD at McGill. However, most revealing was Alan's assertion that Halifax, the home of his own university, was a town built on Bliss, or at least its ancestral line.

Tea was duly taken before the gathered throng returned to hear from an Ashes-less visitor from the University of Melbourne. Chris Reid's talk focused on optical investigations of that less Bliss-ful form of LTP seen at mossy fibre synapses. Chris described the potential unsilencing of active zones during this form of LTP, which might strike a cord with those searching for unifying theories of synaptic plasticity wherever it might happen. More importantly, Chris reminded us all of what is clearly a remnant of Tim's halcyon days (i.e. his Mini). Chris's recollection of that first car ride with Tim struck a cord with those who were privileged or unlucky enough to accompany the renowned hippocampologist as he 'scooted' from the heights of Mill Hill into Town for a social and/or scientific meeting.

Our final speakers were certainly among the best dressed and were much more restrained in a sartorial sense than our retiree. Antonio Malgaroli (Universita' Vita-Salute San Raffaele, Milan) described peptide-based reagents that could be used to fluorescently mark important synaptic compartments with a view to achieving further real time images of synaptic function. The finale came from Nigel Emptage, who further evidenced Tim's penchant for the life at sea by providing pictures of a wet- suited Professor. Nigel's talk described work honed during his time as a post-doc with Tim and he detailed how variations in the optically recorded pre-synaptic responses could be used to provide

further insights into NMDA receptors. The observations discussed by Nigel led him to make the case that NMDA receptors, the post-synaptic guardian of LTP induction, may also be present in the pre-synaptic compartment. Overall, the presentations, scientific content and ambience of contributions made for a most satisfying and educational symposium and one worthy of Tim's contributions to the field.

However, as intimated above, the day was to reflect more than the sum of Tim's scientific contribution. Accordingly, the science was followed by a most cordial social soiree that included Pimm's served by 'boater clad dandies', a jazz band, a Shakespearean play (Melvyn Sherwood Productions) and the acceptance speech from the 'belle of the ball. One would be failing the wider community if one did not mention the outstanding thespian performance of Mick Errington, the young Bliss's long-standing able assistant and doyen of *in vivo* LTP. Mick had come out of his own retirement to tread the Mill Hill boards. His performance was only surpassed by the beautiful and vivacious pantomime dame Ophelia, as played by Abdul Sesay, who reduced many a watching man to tears.

Having received thanks and a gift from John Skehel (Director, NIMR), Tim was left to add his own words to the day. The premise of the speech was that he would speak for longer than his former colleague, the recently retired Errington. Anecdotes were told, points of contention clarified, collaborators and co-workers thanked, mentors homaged, absent friends remembered and loved ones bowed to. It was well received, warmly applauded, its wit, length and grammatical precision noted. The scientific contribution of the speaker is clear. But importantly, as Tim stepped into retirement, the good manners and charm that go with his scientific contribution will be among the longest lasting of memories.

Samuel Cooke
Massachusetts Institute of Technology, Cambridge, MA, USA

Vincent O'Connor
University of Southampton, Southampton, UK

World Congress to focus on advances in research methods and strategies

The 6th World Congress on Alternatives and Animal Use in the Life Sciences (www.knt.co.jp/ec/2007/wc6) will be held in Tokyo from 21 to 25 August 2007, providing a platform for advanced research strategies and methods with the potential to enhance biomedical research and make better provision for animal welfare. It is an opportunity for the international scientific community to celebrate, publicise and share its successes and continue to make progress in these areas.

Fundamental and applied research are essential to provide new insights and to devise and deliver improved healthcare technologies and other societal benefits, and animal research continues to play a vital part in achieving these ends.
It is generally accepted that good animal welfare and good science are inseparable, and that one of the hallmarks of good science is that unintended variables such as animal welfare issues do not go unrecognized or uncorrected.

Whilst we seek every opportunity to present new scientific findings, the constant improvements to research methods are often given insufficient prominence in the mainstream literature.

Asking scientists how progress with alternatives and the 3Rs are relevant to their research often produces only defensive general statements relating to abstract potential benefits, but few concrete examples: whereas asking how research methods have evolved or improved often produces enthusiasm and practical examples of technical progress that can be cross-referenced to the 3Rs. Investment in and progress with alternatives does not impede scientific progress – it promotes it.

The 3Rs – Replacement, Reduction, Refinement

Developing and employing improved research methods, which reflect elements of the 3Rs, are an essential component of mainstream science. 'Alternatives' is not a separate discipline or agenda led by those with an anti-science or ethical agenda. Progress in the 3Rs is led by the scientific community - seeking to look beyond the scope and limitations of existing research methods, to overcome technical problems, and produce more relevant and timely outputs. It is science led and science driven.

Even in the absence of ethical and animal welfare considerations, scientific progress requires that the 3Rs should be embedded in the planning and conduct of biological research.

The 3Rs in practice

Many replacement alternatives are developed initially to obtain general insights or to inform in-house decision making (with the methods are often quicker and cheaper than animal studies).

The use of the term 'reduction' is misleading and wrong – what is actually meant is to minimize or optimize animal numbers. Even if fully implemented, minimization and optimization can be consistent with a rise in the number of animals used if more or better science is the product.

Taking care to optimize and minimize the numbers of animals used is part of good scientific practice. Using too many animals is to be avoided – but using fewer than are required to draw sound conclusions is a much more serious problem in scientific terms. At best using too small a sample size will, if recognized, require additional studies are undertaken if valid conclusions are to be drawn. At worst the problem will not be apparent and misleading statements will be accepted at face value: to the detriment of science if, for example, differences reported as not reaching statistical significance are the result of too small a sample size rather than there being no true meaningful difference.

There is a still a tendency to consider refinement only to be the measures, such as the implementation of humane endpoints, taken to reduce or minimize the pain, suffering distress or lasting harm caused by animal experiments – that is minimizing the harm done. We must look wider than this in considering refinement and consider it to embrace the promotion of good animal welfare – not simply removing the negative, but seeking to add additional positive measures to further enhance animal welfare and improve the science.

Closing remarks

All scientists must keep abreast of technical progress and continue to innovate; and continued professional development must look beyond individual scientific disciplines into other areas where new ideas, knowledge and practices can improve scientific outputs. 'Alternative' methods are more often existing good practice, or 'advanced' methods destined to become integral parts of good science. The 6th WC will focus on aspects of training, experimental design, animal and non-animal models, and data analysis with the potential to improve science and animal welfare. It is an opportunity to celebrate and publicise the progress that is made and the scientific and societal benefits this brings. If you think you have already made significant progress, or have nothing more to learn, then come to the 6th WC to contribute and tell others how to do as well. If you can see room for improvement come to 6WC to listen and learn.

Jon Richmond
Home Office Animals Scientific Procedures Division, London, UK

Let's talk about science...

Rehana Jawadwala experiences a Science Communication Workshop

I am on the train returning back from a 2 day workshop on science communication, held in London by The Physiological society. My mind is overloaded with information, ideas, inspiration and an immense sense of enthusiasm. In the past 2 days I have heard interesting thoughts and debates on the roles and responsibilities scientists ought to have in educating the public, informing them, motivating them and, most of all, encouraging a healthy debate among the general public.

This workshop was conducted jointly in association with Sense about Science, Voice of Young Science, UK GRAD and other organisations. To most of us young participants it was time well spent in the company of professionals who are out there doing active work with the public, communicating their own science and that of the national and international scientific community.

The biggest take home message was that we, as early career scientists, matter. I think most of us came with an idea that the media are interested in huge discoveries, novel and ground breaking inventions, and that they would like to cover people who occupy the higher echelons of science, such as, John Mather, Richard Dawkins and James Watson. But that is far from reality. Most science journalists we chatted with were in search of grass root level scientists who would be able to explain new ideas and processes easily to them; they were interested in our view points as much as they were in those of celebrated scientists.

It was refreshing to note that most of the delegates still cherished those early school days and the teachers who infused such enthusiasm into us; the triggers that made us pursue a career in science. By being informed of various government initiatives and programmes to increase motivation for children to take up science as a career, we were made aware of ways in which we can participate through the Science and Engineering Ambassadors and Researchers in Residence schemes, and National Science Week (9-18 March).

For those of us interested in alternative scientific careers, science journalism was suggested as a stimulating career choice. Most of the professional science journalists had some sort of a background degree in a science field and that had facilitated their understanding of the concepts about which they wrote. The view that the PhD is an over qualification for such jobs is rapidly changing and most employers are reaping the benefits of the transferable skills we learn during our research training.

Even though the workshop lasted only 2 days, we all made some really good friends and, most of all, bonded with people with similar ideas, concepts, fears and aspirations. The intellectual debates, laughs and quirky, geeky habits that we shared over wine and Italian food in a lovely pizzeria, tucked behind the Thames is an evening I will cherish.

Rehana Jawadwala
University of Central Lancashire, Preston, UK

To be strong

Chinese PhD student Meihua He's story

If you are an overseas student here in UK, and at the same time, a mother with a 3 year old daughter that you have left behind in your home country, you will understand the feelings that I will try to describe in this article. It is not easy to get supported by the Chinese government to study abroad; it is also difficult to make the decision to leave the family behind. If you were in this situation, what would you do? Family or career, which one is the most important thing in our life? On 10 October 2005, when I took the plane from Beijing to London, it seemed that I had made my choice.

Life in London is not as easy as I had imagined before I came. I was very homesick, I had problems with the language and my accommodation; all these things made my whole world blue. The university accommodation I lived in when I arrived had no internet access, no radio, no TV and no telephone in the room. I had no friends or relatives in this country, so I have never felt so desperate and lonely as during that period and I thought I would not be able to stay here any longer. The only thing I wanted to do was to pack up all my stuff and go back to China forever. Fortunately, I have two nice supervisors who helped me get through that horrible period. My life became brighter when I got familiar with my research project and my surroundings as time went by. But still, I cannot help sometimes feeling lonely. Daytime here is evening in China and vice-versa so I can only call my family during the day. The evenings are the worst because I cannot call home at times when I am alone.

Culture conflict is another difficulty. I moved to a flat with six other postgraduate students coming from six different, mainly European, countries. The first conflict happened when I put a notice up asking my flatmates not to talk loudly in the kitchen after midnight because my room is just opposite and the noise affected my sleep. This irritated them; they thought that putting up a notice was rude and that I should have confronted them face to face. But for me, the notice was the best way to solve the problem as well as avoid embarrassment.

Loneliness and culture conflict are, however, nothing compared to the guilty feeling I have as a mother. Leaving my daughter behind was the most difficult thing for me. It is not easy for them to visit me or for me to go back home often because of finances as well as time – it's a long way to China. The only thing I could do was to promise my daughter, as well as my husband, that we would meet every 3-4 months.

To live through the entire PhD journey, support is necessary – from supervisors, as well as colleagues. Fortunately, I have both, and that makes me feel that living in London is something can be enjoyable.

Physiology for schools and colleges

Welcome to our new education section

I was recently approached by our *Physiology News* Editor, Austin Elliot, about running an education section for this magazine (and writing articles if the volunteers dry-up!). If I'm honest it's always been high on my 'to-do' list, so with a little push from Austin and the next three articles already lined-up, the first edition of 2007 seemed a great time to start.

The education section, for 2007 at least, will focus on secondary education with articles specifically for teachers, technicians and advisors, but in the future I hope to expand this section to include undergraduate education – any volunteers? This first article is a mish-mash of a number of things, so if you're interested in becoming a School and College Associate of The Physiological Society, hearing about the Association of Science Education Annual Conference, finding out more about The Society's new Research on animals DVD *Make up your own mind*, or careers in science for students, please read on.

School and College Associate membership

Physiology is a major component of the secondary school biology curriculum, and The Physiological Society recognises the need to support its teaching. While The Society is already engaged in a number of activities for teachers and students, we thought introducing School and College Associate membership would be a great way of targeting our resources, encouraging interactions between our scientists and schools, and also help us to find out what resources school and colleges would like us to develop. For £15 per annum schools and colleges can enjoy attendance at various teacher and student workshops, receive hard copies of *Physiology News*, career advice, access to scientists (willing to give presentations), online access to Society journals, and more. For further information please contact me.

Association of Science Education (ASE) Annual Conference 2007

The Physiological Society and Biochemical Society stand where the Research on animals DVD *Make up your own mind* was demonstrated.

The ASE Annual Conference is a school educator's paradise with an extensive programme of workshops, courses and lectures, and an exhibition. The Physiological Society, with a number of other organisations, put together a one day programme *Biology in the real world* which took the theory of science and put it into the context of every day life. The aim of the programme was to extend teacher knowledge, providing them with the opportunity to talk to the experts and give them something to take back to the classroom.

Our speaker, co-sponsored by the Biochemical Society, talked about *Diabetes: from Egypt to global obesity*. Stephen Gough's presentation was excellent. He had a true passion for the subject, and the teachers who attended were enthused by his presentation and were lining up to ask questions. For more details of speakers, and several speaker presentations that can be used in the classroom, please visit www.physoc.org/education/ase.

Top: Glenn Clack (left) explaining the process of drug discovery. Annie Duckworth (right) preparing the audience for some hands-on participation. I never thought ecology could be so much fun!
Above: Stephen Gough telling the audience about the first recording of diabetes by Ebers Papyrus in 1500 BC, 'A wasting disease in which the sufferer produces sweet tasting uring'. Yuck ... someone must have tasted it!

Research on animals DVD *Make up your own mind*

The Society, along with several other organisations, has produced a DVD to address the on-going issues of animal research, which can be used for teaching: *How science works – applications and implications of science*. It includes achievements in medical research, animal welfare and the reduction, refinement, and replacement of animal testing. Extras include a suggested lesson plan, classroom activities, topics and resources, and web sites which add to the ethical debate. The DVD received excellent reviews from teachers at the ASE and will be sent to UK schools in March. If you would like to receive a free copy please let me know. To help launch the DVD, scientists will be visiting schools during National Science and Engineering Week (9-18 March) to demonstrate the DVD and facilitate debate. If you are interested in inviting a scientist to your school, or are a scientist who would like to go into a school, please get in touch.

Careers from science

It is widely recognised that there isn't enough science and engineering careers advice available to school students. In November 2006 the Campaign for Science and Engineering (CASE) held an opinion forum event on *Information and advice on careers in science and engineering for students*, which was attended by The Physiological Society. A report follows on p. 38. The Physiological Society is also supporting *Careers from science*, a Science Council initiative which has just been awarded significant DfES funding. The primary aim of this project is to develop a web resource, aimed at students aged 11-19, to increase their awareness of the wide range of career

paths available from studying science, and importantly, make students (and their parents) comfortable about opting for science. A detailed summary of this project will be included in the next issue and a full report will be available on our web site shortly.

What's next?

When is a boring class practical not a boring class practical? Answer, when a scientist can tell you how to use a simple piece of equipment (already available in many classrooms) to get your students thinking and dare I say it 'having fun'.

Donna Brown
Education and Membership Manager
dbrown@physoc.org

CASE Opinion Forum

The Campaign for Science and Engineering (CASE) regularly holds Opinion Forums on a variety of issues affecting science, the output of which is the creation of a report of policy findings and recommendations to help them in their lobbying of Government. The event on 21 November, Information and advice on careers in science and engineering for students, sought to examine the anecdotal consensus within the scientific community that young people often lack good information and advice about careers in science, or have problems accessing information that already exists, throwing up barriers to attracting potentially good students into science and engineering.

The first presentation was from Lord Jenkin of Roding, the former Chair of the House of Lords Science and Technology Sub-Committee, who chaired the influential report Science in Society. The Select Committee had looked at why the public seemed to be getting disenchanted with science. The Committee had not initially intended to cover education, but found when they looked at the evidence that public distrust of science starts in schools, where we had failed to engage the interest of many pupils who saw science as being stodgy, authoritarian and dogmatic.

Schools therefore had a dual role, in enthusing future generations of people who want to practice science, and to engage the understanding and concerned citizen interests of future non-scientists.

The House of Lords report *Science teaching in schools* identifies careers advice as a problem. Students tend to see science and technology as 'hard' subjects, and anxious to get high grades, choose to study 'easier' subjects. Lord Jenkin concluded that students need high quality careers advice long before they reach A level as it is very difficult to change track afterwards, but many teachers don't feel qualified to provide this – we need advisors to support the advisors!

This was followed by a presentation from a chemistry undergraduate, Danielle Miles, whose strong interest and commitment to studying chemistry had not been facilitated by the careers advice she had received in school and elsewhere, or the decline in properly resourced science teaching in schools and universities. There was a strong message here, that had she not been so personally committed to studying chemistry, the present system would not have acted to encourage her into it. Many potential students must be falling by the wayside through similar difficulties.

The final presentation was from Mike Hill of Prospect Services who talked about his many years of being a careers advisor in several different industries. It is important to share good practice and support teachers who are trying to provide an advice service in schools, often as a part-time addition to their many other roles. In his experience job markets can change radically, and careers advice needs to keep up with this.

The reasons why people select particular careers are very complex. Peer and parental pressure are very important. Careers advisors can also be influenced by the apparent glamour of certain careers, overselling options such as studying law, the media, or sports science, without having a sufficient grasp about the real level of job opportunities that are likely to be available. Careers advice needs to provide this, so that students can make informed decisions about the levels of competition that they are likely to face in trying to attain their chosen careers.

Hill stressed that when he is offering careers advice, he tries to encourage people to keep their options open as much as possible. A very important message for students is that studying science and technology opens up 80-90% of the job market, with science graduates being in demand in a very wide range of industry sectors.

The meeting then split into workshop groups to discuss the roles of central and local government and schools and colleges, and the responsibilities of industry and the wider scientific community.

A lively debate ensued. It was felt that government had an important information co-ordinating role. Employers and young people were confused by many different sources of information. SETNET was regarded as being a model national scheme, and could become the central vehicle for providing careers advice and support to young people and teachers. A simple pack of information on science for teachers to help dispel myths might be very effective, with a strong message about the wide variety of careers open to people who do science subjects at school and university. Strong role models, preferably highlighting young scientists to make them accessible, should be promoted to help challenge stereotypes.

Older people's needs should also not be forgotten; we should aim to re-attract people to science by offering re-training for career changes.

Parents need to be encouraged to be more involved in the careers advice process, after all parents are already established in a wide variety of different careers and could be a good resource.

Careers advice in schools needs to become a central part of the schools activity, not just an add-on. Teachers need more training in providing careers advice, perhaps this could be consistently provided through the network of Science Learning Centres? Careers advice for students needs to start as early as possible and be accessible at each stage of the learning process. Companies are often keen to work with schools in offering careers advice but don't know how to access the school system. A one stop shop facilitating that access, such as SETNET, would be very useful.

Liz Bell
Head of Policy and External Affairs

Bernard Katz

Liam Burke recalls an 'annus mirabilis' during his time in Bernard Katz' laboratory

In September 1952 Bernard Katz invited me to join his laboratory in the newly created Biophysics Department at University College London. I had just completed my BSc at UCL and was uncertain what my future would be. I was Katz' second choice, his first choice having turned the job down. That I was even in second place was due to a recommendation from G L Brown, Head of Physiology, with whom I had a good relationship (we had a similar sense of humour, somewhat larrikin). I could not believe my good fortune but I was apprehensive about my performance under the eagle eye of Bernard Katz.

1952 was an 'annus mirabilis'. This was the year in which Hodgkin and Huxley published their seminal papers on the ionic theory of the action potential. It was the year in which Eccles and colleagues published their equally important papers on synaptic transmission at the motor neurons of the spinal cord. It was the year of Eccles' Waynflete Lectures in Oxford, subsequently published as *The neurophysiological basis of mind*. That year saw a series of important meetings, most notably one at the Royal Society in which all of these recent advances were described, discussed and celebrated. It was also the year in which Charles Sherrington died and somehow his departure was fitting because the first half of the 20th century had been dominated by the Sherringtonian revolution and this was now over. Sherrington's work, encapsulated in two epoch-making books, *Integrative action of the nervous system* (1906) and *Reflex activity of the spinal cord* (1932), the latter written in collaboration with Creed, Denny-Brown, Eccles and Liddell, based largely on his work on spinal reflexes, brought order out of chaos for the physiology of the central nervous system. Now, in 1952, just half-way through the century, there was to be another change of paradigm. The second half of the 20th century was to be dominated by ionic mechanisms and facilitated by the invention of the microcapillary microelectrode. This electrode, developed in Ralph Gerard's laboratory, was used to brilliant effect by Katz and Paul Fatt in their famous 1951 paper, ushering in the new age.

Bernard Katz in 1952 when Liam Burke joined his laboratory (© Godfrey Argent, for the Royal Society)

So this was the setting for my initiation into neurophysiology. I could truly say, with Wordsworth, 'bliss was it in that dawn to be alive'. Katz had attracted some brilliant people to his laboratory, for example, Ricardo Miledi, Jose del Castillo, John Nicholls, Ove Sten-Knudsen, Bernard Ginsborg, Bob Martin, Ian Boyd, Don Jenkinson, Ed Furshpan and many others after I had left. I made many good friends among that group and still maintain contact with them today. The 4 years I spent in Katz' laboratory were among the happiest of my life.

Katz was a very kind person, aware of his ability but also aware of his limitations, quite humble, not in the least bit arrogant. He was also rather shy so that it was often difficult to maintain a conversation. At first I asked rather a lot of questions, but if he thought I could have worked out the answers by myself he wouldn't give me the answer. He would say 'You can look that up in …'. Like most students I was lazy and was always looking for the easy way out. But Katz' attitude was good pedagogy. It reflected his own upbringing. He was the epitome of the self-taught man. Sometimes I felt he did not know the answer to my question but it was more likely that I was not expressing myself well.

Katz was always rather tense, rarely relaxed. In those days we had to make the microcapillary electrodes by hand. This was done by holding a piece of glass capillary tubing with two hands and placing the centre of the tubing in the small hot flame of a Bunsen burner. At a critical moment when the glass had softened enough, a sharp pull produced two electrodes. Too soon or too late in pulling was disastrous. Our best electrode maker was del Castillo, a very relaxed Spaniard. Katz strove valiantly to make electrodes but his temperament was a major obstacle and with each failure he would get more and more angry, eventually abandoning the attempt and stalking off fuming. Otherwise Katz was not often angry. Indeed, I remember clearly only one other occasion, when a paper was published claiming that the records in the 1951 Fatt & Katz paper were artifacts. Katz hit the roof.

Everyone has their foibles. When I was in his laboratory Katz would not send a reprint to anyone unless the request was hand-written. This reflects an old-world courtesy which has now almost disappeared. I don't know what Katz would make of the present-day world of emails when even members of your own family send you computer-generated letters with no signatures.

Katz was a refugee who became more English than the English. He modeled himself on A V Hill under whom he did his PhD at UCL. A V assisted Katz (and many other refugees) before, during and after the Second World War. At one time A V decided to sell his car, an old Austin A40. Katz bought it. His reverence for A V was such that he would have paid a fortune for that car. If he had been given a choice between that car and a Nobel Prize he might have chosen the car (but A V wouldn't have allowed that). Katz couldn't drive but soon learned under the tutelage of Bob Martin. When A V died in 1977 Katz wrote his obituary for the *Biographical Memoirs of the Fellows of the Royal Society*. Many of the expressions Katz used about AV could be applied to himself. ' … he was intolerant and scornful only of pretentiousness and intellectual snobbery.' '(he) was held in the greatest affection … for setting … an example of uncompromising integrity in personal and social relations.' '(he) was a person of old-fashioned tastes and virtues, addicted to simple commonsense and straight dealings, and very allergic to pomposity.'

Liam Burke
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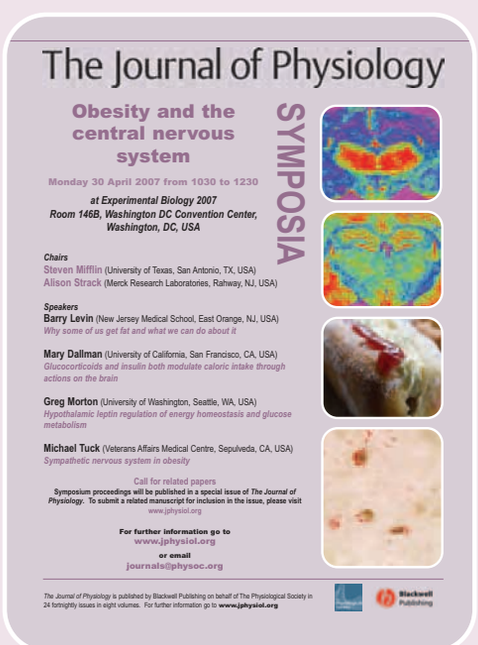
The Journal of Physiology



SYMPOSIA

The Physiological Society

Blackwell Publishing

Symposia 2007

Friday 2 March
Regulation of ion channels and transporters by phosphatidylinositol 4,5-bisphosphate (PIP_2)
At the 51st Biophysical Society Annual Meeting
Room 316/317, Baltimore Convention Center, Baltimore, MD, USA

Monday 30 April
Obesity and the central nervous system
At Experimental Biology 2007
Room 146B, Washington DC Convention Center, Washington, DC, USA

Wednesday 2 May
Exercise hyperemia. Are there any answers yet?
At Experimental Biology 2007
Washington DC Convention Center, Washington, DC, USA

July
Brain adaptations for a successful pregnancy
At the IBRO World Congress of Neuroscience (12-17 July)
Melbourne, Australia

Thursday 19 July
The cortex, interneurones and motoneurones in the control of movement
At the IBRO World Congress of Neuroscience
Darwin, Northern Territory, Australia

For forther information go to
www.physiol.org
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The Journal of Physiology

Symposia

Since 1999 *The Journal of Physiology* has run symposia at major international meetings (http://jp.physoc.org/misc/symposia.shtml). These have been successful in raising the profile of *The Journal* and the resulting Symposium Reports have been amongst the most-read and -cited in *The Journal*. One of the dilemmas of the Editorial Board of a journal that covers all areas of physiology is where to focus attention. The Symposium Issues are markers for specific areas of expertise on the Board and emerging topics. In 2007 six symposia in different areas are being sponsored by *The Journal* (see facing page). *The Journal* is increasingly interested in attracting high-quality related research papers to accompany these reports, with the aim of creating an informative issue that covers a number of approaches and includes the latest research results on a particular topic. Calls for related papers are put out on the web site (http://jp.physoc.org/misc/callforpapers.shtml) and email alerts, and are sent out to relevant email lists. Society Members can act as ambassadors for *The Journal* by passing on information about the symposia and the calls for related papers to colleagues who may be interested, and indeed should consider attending the symposia and submitting related research papers for inclusion in the Symposium Issues themselves. When the new Society web site is unveiled the Editorial Board hopes that opportunities for further interaction with Members about *The Journal*'s symposia and overall content will arise.

The Journal is also planning an Olympics Special Issue for January 2008, which will take advantage of, and enhance, *The Journal*'s reputation as the top journal in integrative (especially human) physiological research. There will be a number of invited reviews focusing on issues in integrative physiology with a strong link to human performance. A call for related research papers for inclusion in this issue is being made on *The Journal*'s web site and it is hoped that this will be an important source issue in the field. The deadline for submission of original research papers for this issue is 1 July 2007.

Carol Huxley
Managing Editor

New Editor

New *Journal of Physiology* Editor Ingrid Sarelius (above) graduated with a PhD in Physiology from the University of Auckland, New Zealand, in 1978. She was a Fogarty International Exchange Fellow at the University of Virginia from 1979-1981, and joined the University of Rochester in 1981 as Assistant Professor in Biophysics and in Physiology. Ingrid is currently Professor in Pharmacology and Physiology and also in Biomedical Engineering at the University of Rochester, Fellow of the Cardio-vascular Section of the American Physiological Society and a Fellow of the American Heart Association. Ingrid has also served as a Past President of the Microcirculatory Society, and is currently Chair of the Microcirculation Section of the IUPS Commission on Circulation and Respiration. She served on the US National Committee of the IUPS from 1996-2005 and serves, or has served, on the Editorial Boards of the American Journal of Physiology: Heart and Circulatory Physiology, Microvascular Research, and Microcirculation.

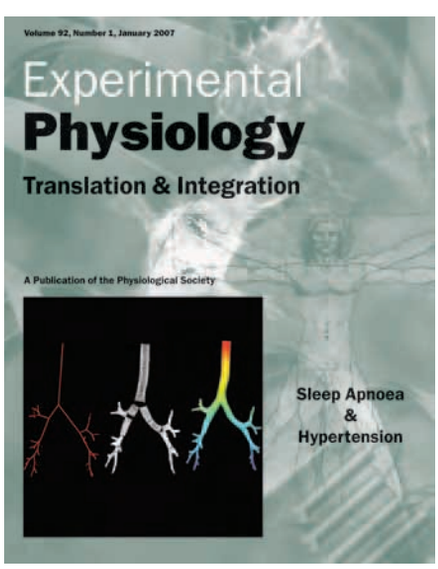
Ingrid's research focus is on cell communication in the microvasculature, with two major areas of interest. First, mechanisms of metabolic responses in small arterioles, focusing on the role of endothelium, and endothelial cell calcium, in metabolic vasodilation and the exploration of mechanisms underlying the axial communication of metabolic dilations along the microvascular wall in situ. Her second interest is in leukocyte-endothelial communication during inflammation, including regulation of permeability. Ingrid's laboratory has a long-standing interest in microvascular hemodynamics, particularly as this relates to understanding the role of shear forces in adhesion molecule expression and leukocyte interactions with the microvessel wall.

Experimental Physiology
Translation & Integration

Sleep apnoea and hypertension: physiological bases for a causal relation

In the spirit of *Experimental Physiology's* commitment to address integrative and translational physiology, the January themed issue provides a series of review articles which bridge cellular and molecular mechanisms of physiological adaptations to intermittent apnoea to the strong clinical association between sleep apnoea and hypertension (http://ep.physoc.org).

Sleep apnoea, once thought of as a disease of morbid obesity, but now recognized as a prevalent disease that is a significant risk factor for many serious comorbid conditions with cardiovascular disease. This field of investigation has evolved from the clinical observation of a strong association between sleep apnoea and hypertension, to epidemiological data reported in the 1980s. From these clinical observations several



lines of investigation have emerged to test whether there is a causal relationship. The resulting literature has consistently shown that intermittent apnoea, in particular intermittent hypoxia, is the primary culprit in the physiological changes accompanying sleep apnoea which provoke the increased risk of hypertension. How this unique stimulus leads to physiological adaptations that can culminate in hypertension has been the focus of intense investigation over the past 15 years.

The primary physiological mechanism linking sleep apnoea and hypertension is the well-established chronic elevation of sympathetic nerve activity (whether measured by circulating catecholamines or by microneurography) that is present during sleep and wakefulness. This often rivals the activity seen in patients with congestive heart failure. Acutely, apnoea leads to increased sympathetic nerve activity by activating the arterial chemoreceptors and by withdrawing the respiratory modulation of sympathetic discharge. This has led to the hypothesis that the chemoreflex is, in part, responsible for the chronic elevation of sympathetic activity. Consequently, a major focus of this themed issue is on the manner in which the chemoreflex adapts to intermittent hypoxia or apnoea. A hallmark of essential hypertension is vascular dysfunction, and there is now a growing body of evidence suggesting that intermittent hypoxia can lead to vascular dysfunction. Last, since hypertension is a core disease process integral to the metabolic syndrome, the possible links between sleep apnoea and the metabolic syndrome are addressed.

The clinical link between sleep apnoea and hypertension involves partly the comorbid states associated with sleep apnoea; however, evidence is growing to support a causative role of sleep apnoea. The evidence for this and some of the potential mechanisms, including the role of altered chemoreflex function in patients and the potential link to specific neuromodulators such as angiotensin II and endothelin, is reviewed by Weiss *et al*. Brainstem processing of chemoreceptor afferent input is the primary target for both short-term and long-term adaptations of respiratory control. Long-term facilitation of respiratory control is a model of central adaptation which appears to play a role in the occurrence and/or protection against apnoea as reviewed by Mahamad & Mitchell. Since sympathetic efferent activity is chronically elevated with non-sustained intermittent hypoxia, it is likely that altered brainstem processing may be a contributing factor. How the adaptive mechanisms for respiratory control and sympathetic neural control are related is an important target for future mechanistic investigations. The evidence that chemoreflex function is affected by intermittent hypoxia or apnoea is consistent in both animals and humans. Prabhakar *et al.* review the specific adaptations which occur at the carotid body receptors and demonstrate that there is altered afferent neural regulation from the chemoreceptors *and* altered processing within the central nervous system. These investigators also provide compelling evidence for an important role of reactive oxygen species and hypoxia-inducible factor-1 in the cellular and molecular signalling mechanisms linking intermittent hypoxia to sustained sympathoexcitation.

Considerable data from humans also confirm that chemoreflex control of sympathetic activity is altered with intermittent hypoxia or apnoea. The potential mechanisms that have been explored include altered gain, resetting and sustained chemoreceptor activation. These potential mechanisms and how they may contribute to the chronic elevation of sympathetic activity are reviewed by Smith & Pacchia and Weiss *et al*. For these changes in neural control to translate into essential hypertension, sustained alterations of cardiac, renal and/or vascular function must occur. Consistent with most forms of hypertension, evidence is accumulating to suggest that endothelial dysfunction and impaired vascular control are a consequence of intermittent hypoxia and thus are likely to comprise a causative outcome linking sleep apnoea to hypertension. Foster *et al.* review the evidence supporting this premise. Finally, the relationship of sleep apnoea to hypertension combined with its association with obesity and diabetes implies that sleep apnoea is likely to grossly increase the risk of the metabolic syndrome. In fact, sleep apnoea should perhaps be considered a component of the metabolic syndrome. The final review by Wolk & Somers explores the strong evidence linking sleep apnoea to obesity, insulin resistance, diabetes, lipid dysfunction, inflammatory disorders and hypertension, and thereby provides a compelling argument for its role in the metabolic syndrome.

This themed issue provides a foundation of the primary mechanisms that appear to link sleep apnoea to hypertension and to the metabolic syndrome. As future research extends these findings, this foundation of knowledge will provide not only the catalyst for better understanding of these causative relationships, but also the potential for new strategies for treating hypertension and the other disease processes of the metabolic syndrome.

Michael L Smith
University of North Texas Health Science Center, Fort Worth, TX, USA

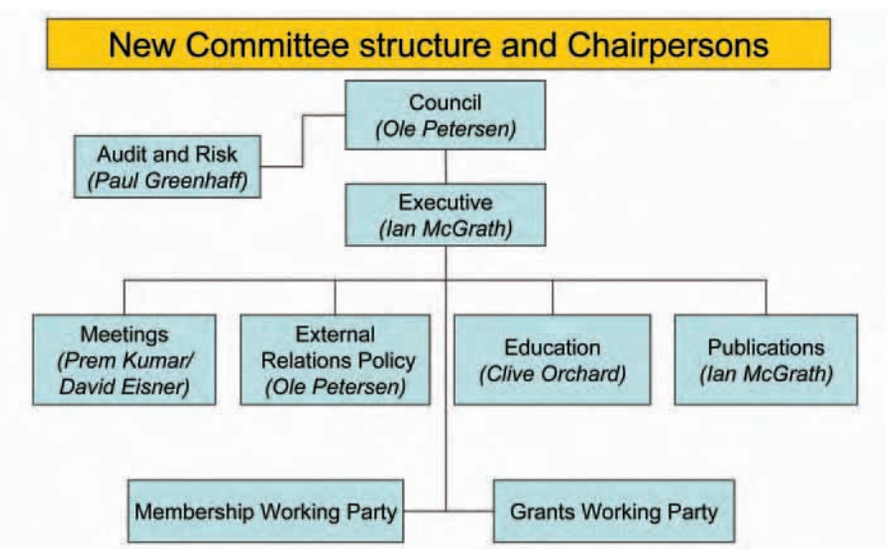
What's happening in The Society

The first of a regular series of short updates to keep you, the Members, informed of the priorities and activities of the Council and Executive Committee of The Society

Two projects that were approved last year are now coming to fruition. You will have seen the new Society logo in the last edition of *Physiology News* and it will be appearing on all Society documents in the coming year. Development of the new web site is well advanced with launch expected in early 2007.

At its recent meeting, the Council approved a streamlined committee structure for The Society which aligns with the various functional groups in the London and Cambridge offices (see Fig. 1). A significant change is to combine the International and Meetings committees into one, which will cover all such scientific events whether held in the UK or abroad. The formation of a new Publications Committee is also an important step, prompted by the need to take an overall view of The Society`s publishing activities. We produce two prestigious journals, *Physiology News* magazine and are planning a textbook series. This new committee will take a strategic view of all our publication activities and of our interactions with publishers. The latter is particularly timely as our current publisher, Blackwell, has just been taken over by Wiley and we will need to monitor what effects this will have. There are many challenges approaching in the publishing arena; the introduction of new technologies, the steady decrease in requirements for hard copy publications and the threats from open access (see previous *Physiology News*). The Publications Committee will address all these issues and develop an overall strategy for publications from The Society. In parallel with this revised structure, committee membership is also being reviewed and modified in order to have the required spread of expertise and to keep numbers to an optimal level.

An important topic at the recent Council meeting was Society finances and the budget for 2007. Our financial state is reasonably healthy with income showing a small rise, however, this is less than inflation. There are a number of financial exposures and risks on the horizon for which we need to budget. The Council agreed to put aside £400,000 this year into a contingency fund for the IUPS meeting we are hosting in 2013. The plan is to put further sums in reserve in coming years until we have a total fund of £1 million, to underwrite potential commitments associated with this meeting. A very significant risk for our future finances is the loss of journal income, if open access dramatically reduces subscriptions. To protect the future activities of The Society, we plan to supplement our reserves by depositing additional sums and re-investing income from our current investments to build a fund sufficient to generate about £500,000 p.a. This would enable The Society to continue some of its core activities in the face of a precipitous fall in journal income. A working party has also been formed to evaluate other alternative sources of income for The Society.



Summary of the new committee structure and chairpersons. The activities of the Membership Services Committee will be continued by the Membership and Grants Working Parties, which will report to the Executive Committee. Other committees also have associated working groups, which are not shown on this figure for simplicity.

A number of you will be only too familiar with the problems we have had with the PO Box used for Society correspondence. In this age of technology, it is amazing that a simple mechanism such as a PO Box can lead to so much misdirected mail! Despite numerous phone calls of complaint to the Post Office, we have concluded that the drawbacks of the use of a PO Box number outweigh its benefits and the new web site will give the Peer House street address for all correspondence. The PO Box will continue to 'operate' in parallel with direct addressing for a period of time.

As a Society we are always looking for ways to improve the quality of our activities, to be more efficient and to provide better services to our membership. Some of the projects underway to achieve this are: a review of our strategic objectives and of the role of Council, a project to develop physiology teaching resources for secondary and tertiary levels and a new DVD on the importance of animal experiments in advancing medical advances. Pilot projects have also started to evaluate new membership categories, which could build the critical mass of Society membership and increase the awareness of physiology as the fundamental science of life. Plans are well advanced for our main meeting in the summer which will be the first combined event with our colleagues from the Biochemical Society and the British Pharmacological Society. It will be **the Bioscience** meeting in Europe next year and one that you cannot afford to miss!

Michael Collis
Chief Executive

Society Meetings

New Society Meetings Secretary Prem Kumar looks to the future

Figure 1. The Meetings Secretary, Prem Kumar (on the left) and the ex-Chair of The Society, Giovanni Mann do their Deputy Dawg impressions at the foot of the Great Wall of China on a break during an invited visit to the Chinese Association of Physiological Sciences Meeting in Beijing, November 2006.

In July 2006 at the AGM of The Physiological Society, I was elected Meetings Secretary – a post that I am very proud to hold. This followed 'shadowing' Bridget Lumb during her last year in this position and I am grateful for her time and energy in helping me move smoothly into the role. It doesn't seem so long ago that I gave my first oral communication to The Society (although I suppose 22 years is a long time!) and the responsibility can still sometimes seem daunting. Certainly, academic life is quite different now than it was back in the 1980s. I am aware that, with time now being such a precious commodity, only high quality meetings will be well attended and I hope that I am able to produce these on your behalf. Fortunately, an excellent events team in the London office, headed by Nick Boross-Toby, provides all the support I need. Nick (whom I am sure many of you have met or corresponded with) and his team look after the day-to-day running of meetings, freeing me up to concentrate on strategic developments in consultation with my colleagues on The Society's Executive Committee and Council.

Meetings are the most obvious facet of The Society's many functions. We now have an established system, with an annual main meeting complemented by smaller, focused meetings, and this system is, I believe, slowly bedding into your consciousness. A clear list of scheduled Society meetings, and also of meetings that we are associated with (through *The Journal of Physiology,* collaborations with other societies or part sponsorship of other physiology-related meetings) is available at http://www.physoc.org/meetings. The list is long and covers a wide range of topics. Together with a generous grant support scheme, it should be possible for all Society Members to attend some meetings of interest each year to which The Society has contributed.

The Society held its main meeting in Bristol in 2005 and UCL in 2006. This year we will meet in Glasgow (9–12 July) as part of the LifeSciences meeting (www.LifeSciences2007.org), in collaboration with the Biochemical and British Pharmacological Societies. Free oral and poster communications will be run alongside high quality international symposia and the range of themes should cover most of our Members' interests. This exciting new venture will be viewed by all three societies as a possible template for future collaborations and I hope that our Members will make every effort to attend to ensure its success. It is the hope of the LifeSciences Scientific Committee that all symposia will be attended by some members from all three societies, as the distinctions between biochemistry, pharmacology and physiology become increasingly blurred. There will be a cost to all those attending the meeting. I appreciate that this is something we have not had to consider previously, but as both the BS and BPS always charge a registration fee, we have been requested to follow suit. That said, Society meetings have stood out for being the last of the free (i.e. no registration fee) meetings on the international circuit (at least to my knowledge). It may be that we should consider this carefully in the future if we wish to produce high quality meetings in light of any potential shortfalls in our income due, for example, to open access publishing. But I would expect that any fee charged after Glasgow would not be substantial (i.e. relative to the costs incurred in travel and accommodation). Presently, a registration fee of £50 for full Members and £25 for Affiliates is something that the Meetings Committee is considering for main meetings. I understand that any increased cost is unlikely to be welcomed and I shall keep you all informed of developments.

2007 also sees a series of excellent focused meetings – in Edinburgh, Belfast, Manchester and Bristol – covering topics that include perinatal physiology, ion channels, cardiac and renal function. I strongly recommend anyone who has not yet attended a focused meeting to make an effort to do so, as they are well worth the time, and the opportunity for interaction with colleagues is a particular strength of the format. I have attended several recently and I am grateful to all the local organisers for their efforts and enthusiasm. Speak to someone who has attended a focused meeting - they will be very supportive of the concept, as it appears to fill an important niche between the major meetings on the international circuit (e.g. EB, Neuroscience, ATS, etc.) and the much smaller, often invitation-only, ones that not everyone can attend.

Looking ahead, the main meeting in 2008 will be at the University of Cambridge and the deadline for

Table 1. Consolidation of Special Interest Groups (SIGs) of The Physiological Society into themes. The present list of SIGs are shown, abbreviated in rows, and each is associated (with a X) to a number of themes (listed in columns) that cover the range of interests of Members. Each SIG is associated with two or more themes and each theme has a significant number of SIGs associated with it. This matrix is not definitive, but should provide a starting template for how future, non-main, meetings might be organised around themes rather than SIGs.

	Cellular neuroscience	Integrative neuroscience	Cardiovascular, respiratory & autonomic control	Human physiology & exercise science	Epithelia & membrane transport	Microvascular & endothelial	Smooth muscle	Cell signalling	Cardiac
BBB	x		x			x		x	
CRAC	x	x	x			x			
CN	x		x					x	
CS	x					x		x	
CIN	x	x	x					x	
CP	x	x	x	x	x	x	x	x	
DP	x							x	
EMT					x		x	x	
GIT					x		x	x	
HCM			x			x		x	x
HP		x	x	x		x			
IC	x		x		x	x	x	x	x
L		x		x					
MEP			x			x	x	x	x
MC				x			x		x
NE		x						x	
PP			x		x	x	x	x	x
RP			x		x	x		x	
Resp		x	x						
SMC	x	x		x				x	
SF	x	x						x	
SM						x	x		
SSP	x	x		x				x	
TW	x	x	x	x	x	x	x	x	x

BBB Blood brain barrier; **CRAC** Cardiovascular, respiratory & autonomic; **CN** Cellular neurophysiology; **CS** Cellular signalling; **CIN** Comparative & invertebrate neuroscience; **CP** Comparative physiology; **DP** Development & plasticity; **EMT** Epithelia & membrane transport; **GIT** Gastrointestinal tract; **HCM** Heart & cardiac muscle **HP** Human physiology; **IC** Ion channels; **L** Locomotion; **MEP** Microvascular & endothelial physiology; **MC** Muscle contraction; **NE** Neuroendocrinology; **PP** Placental & perinatal physiology; **RP** Renal physiology; **Resp** Respiratory physiology; **SMC** Sensorimotor control; **SF** Sensory functions; **SM** Smooth muscle; **SSP** Somatosensory physiology; **TW** Teaching workshops.

symposia applications will have passed by the time this magazine is published. We have already begun preparations and I am very hopeful for an excellent meeting in attractive surroundings. More details nearer the time, but please try to keep 14–16 July 2008 free in your diaries. Although the annual meetings may appear to be symposia-driven, there are many free oral and poster communications that are organised through our Special Interest Groups (SIGs). We have recently held a number of SIG convenor elections and I am looking forward to working with all the convenors to ensure high quality sessions. I expect to increase the number of slots available for oral communications at Cambridge as this is something that some Members have requested and it seems reasonable to try to accommodate this. If you wish to present on any topic, I can guarantee (provided it is ethical and has scientific merit) that it will be timetabled. There is no reason why any Member should not be able to present original work at the annual meeting and if you wish your SIG to be more active, pester your SIG convenors – or me!

A call for a venue and host for the 2009 main meeting will go out during March 2007 and I hope that we are able to attract a number of high quality bids. If you want The Society to spend some sunny days at your site, please download the forms in March, talk to the relevant people in your institution and send in an application. Please don't hope that someone else will do it for you and remember that our events team now handles much of the organisation and administration and your department need no longer close down for the duration of the meeting!

Some Members have raised concerns about a reduced opportunity to present oral communications within the new format of meetings. I hope that a subtle change might begin to address this. Thus, from 2008, we will begin to see what will be called 'themed meetings' rather than 'focused meetings'. Briefly, the aim is to run (in addition to the main meeting) four, 3 day meetings each year, based around a single, focused symposium but, in addition, with space allocated for free communications to be presented within a physiological 'theme'. Table 1 shows a matrix with all current SIGs in rows and a smaller set of themes in columns. Themes have been determined on the basis of our Members' interests and are not as arbitrary as they might seem at first glance! From the matrix, you can see that all SIGs fit into two or more themes (Xs in rows) and each theme has a minimum of six associated SIGs (Xs in columns). Bids to hold themed meetings will be selected by scientific quality and timeliness of the symposium proposed. I believe strongly that the scientific quality should take priority in our selection process and will be using external review processes to ensure the quality is as good as it can be, perhaps, for example, by suggesting alternate or additional speakers. Of the 3 days of a themed meeting, the symposium element will fill no more than two thirds of the time available,

with the remaining time devoted to free communications from any SIG linked with the theme. One aspect of themed meetings is that there will be no parallel sessions and attendance is limited to between 100–200 people. In addition, themed meetings need not be held at a university if a cost effective alternative (and, hopefully, attractive) venue can be found. There are many of these places around the UK and it should make for greater interest if we meet in different surroundings from those in which we usually congegrate.

Perhaps an example may make things clearer. Let's say someone was successful in a bid to hold a themed meeting in 2008 under the theme of *Cardiovascular, respiratory and autonomic* with a symposium on, for example, *Ion channels, mitochondria and O_2 sensing*. This might involve around 12 speakers being invited to talk at the symposium – selecting from a range that includes not only the key, recognised physiology PIs in this field but also young investigators and perhaps clinical staff and researchers from other disciplines (biochemistry, biophysics, engineering, mathematics, etc. as appropriate) to produce an interesting mix of cutting-edge talks that should enable full discussion on the topic. In addition, posters and oral communications would be submitted that allied with the symposium topic, but also any posters and oral communications from the eight SIGs associated with this theme (see Table 1) would be appropriate. It would be my job – with Nick Boross Toby and Heidi Adnum in the London Office, the symposium organisers and related SIG convenors – to produce a programme that accommodated all submissions appropriately. If, for example, one day were put aside for free oral communications only, this would provide around 28 15 minute slots in addition to the posters and any selected, symposia-related orals. If this were to be held at Birmingham, for example, the meeting might be held within the conference facilities of our excellent City Botanical Gardens with the main dinner perhaps on a canal boat. I promise you, I haven't arranged such a meeting – but it does sound like one I'd attend! Themed meetings should thus provide an opportunity, in addition to the main meeting, for free communications to be presented to a large, knowledgeable audience and in an environment that encourages an exchange of ideas. They should also contain cutting edge science and be fun to attend. The aim would be, within any 2 year period, for any Member to be able to present original work at the two main meetings plus at least one, if not two, themed meetings with a mean gap of around 6 months between attendances.

In progress are plans to hold a joint meeting with the Chinese Physiological Society in Beijing during October or November 2008 (see Fig. 1) and a joint meeting with FEPS (perhaps in Scandinavia) during 2010 as well as the IUPS meeting in the UK in 2013. These large-scale ventures are an exciting opportunity for our Society to interact on an international scale and to showcase our strengths.

Of course, the success of the meetings depends, ultimately, upon Members submitting great ideas for symposia, for themed meetings and free communications arising from original work and I hope that many of you will be encouraged to apply or to submit original work to either the main meeting and/or the themed meetings. I am optimistic for the future of our meetings and hope that optimism is shared by many of you. The annual calendar of meetings (see the Society web site) contains information on the dates of all calls and I will ensure that reminders are sent out when appropriate. The forms are very simple indeed to fill in as the London Office does much of the work regarding budgets, etc. What is required is the continued, creative input from the membership to generate high quality sessions. I look forward to meeting Members and listening to any views on how we might improve what we can offer in terms of meetings, but ask only that you appreciate that it isn't possible to please everyone – at least all the time!

Prem Kumar
Meetings Secretary

Are patients safe with the NHS?

This debate was inspired by recent House of Commons Public Accounts Committee comments on safety aspects within the National Health Service:

Every day over one million people are treated successfully by the NHS. Although patient care is generally of a high standard, the scale and complexity of patient interventions means that patients can sometimes suffer unintended harm, and official estimates show that one in 10 patients admitted to NHS hospitals is unintentionally harmed. There were 940,000 reports of incidents and near misses last year, which include blunders ranging from medication errors and drug interactions to missing emergency equipment and the wrong limbs being amputated. Even more patients are at risk since this does not include 300,000 reports of hospital-acquired infections each year including MRSA. Around 50 per cent of all actual incidents might have been avoided if NHS staff had learned lessons from previous ones. There are big differences between similarly-sized trusts in the number of incidents reported. Massive under-reporting of deaths and serious incidents means the NHS has no idea how many people are dying each year from patient safety incidents.

However it was noted that these startling statistics are not significantly different from those reported in several other developed countries.

The debate at the Parliamentary and Scientific Committee on 20 November

asked 'How can the further application of science, technology and engineering help to improve a situation arising predominantly as the result of human failure?' Lively discussion of this important issue was kicked off by presentations from Bill Murray (Acting Chief Executive of the National Patient Safety Agency), Tom Treasure (General Thoracic Surgeon, Guy's Hospital) and Peter Buckle (Robens Centre for Health Ergonomics, University of Surrey).

Bill Murray, an engineer by background, said that the National Patient Safety Agency, a separate organisation from the DoH, was founded in July 2001 in recognition of the fact that although NHS safety records were respectable by international standards, improvements were possible, and it was important to implement systems where patient safety could be improved by learning from experience. The NHS is a very complex system, but it should be possible to learn from other industries. For example, it has often been found in the analysis of major accidents such as the Challenger disaster, that the problems arose from the complex interactions of multiple factors rather than a single cause of failure such as one individual. Similar systems failures can strike the NHS. The NHS is currently trying to emulate the sort of sophisticated safety processes developed in the airline industry, with a focus on trying to build a no-blame culture to increase reporting of incidents in a national reporting and learning system. New integrated risk management approaches also seek to involve patients, their families and the general public in improving systems.

Tom Treasure noted that hospitals, by their very nature, are high risk places. They concentrate sick and dying people alongside strong medicines and sharp instruments. We should focus on the positive – the nation is far safer with an NHS than without one. Analysing what goes wrong in individual cases can be very complex. Surgical cases can be very complicated, and it can be difficult to see which of a long series of treatment steps caused the problem. The system is also skewed in that the very good surgeons tend to work regular daytime hours, with less experienced surgeons handling the difficult emergency cases that tend to appear during anti-social hours. However, it is possible to judge the overall performance of individual surgeons against expected success rates and to challenge 'bad' surgeons. This needs to be a confidential process to encourage surgeons to admit to mistakes and seek further training etc. if necessary. There are also inherent problems in trying to establish an effective national monitoring system, and in particular in trying to set the 'alarms' to flag where action needs to be taken. Like a burglar alarm system, it can't be too sensitive in triggering false alarms, but has to be capable of detecting genuine intruders. He concluded that the NHS needed more safety to be in-built into its equipment and processes.

Peter Buckle stressed the importance of taking an ergonomics approach, designing safety systems with the end user firmly in mind. He works with systems engineers, cognitive psychologists and designers. He gave a very thought-provoking example of how to build in potential errors into prescribing systems, many of which regularly occur. This includes giving medicines similar names and packaging, not putting the name of the drug onto the pills so people forget what they are when separated from their packaging (e.g. by patients putting them into personal pill bottles), putting vital contra-indications information on sheets of paper separate from packaging which patients then throw away, using small font sizes that people with poor eyesight can't read, etc. etc. Yet we expect the right patient to take the right life-saving drug at the right dose at the right time! This can be a big problem for elderly people trying to manage multiple medications, and can have appalling results when it goes wrong. How do we change this? Buckle felt that the NHS doesn't see itself as a high risk industry, yet it needs to if safety issues are to be effectively managed. He noted that the NHS is a very complex system with incomplete feedback between medics, patients, manufacturers, etc. It is important to get people together from different parts of the system to map out and understand each other's problems. We need to really understand what happens in healthcare systems and build in more safety. Ergonomists believe that we should never train people in a system that is intrinsically unsafe.

The ensuing discussion agreed that improving systems was a good idea, but asked where is the balance if we are not to increase NHS overheads too much? The speakers responded by saying that improved safety systems are not necessarily expensive, and are likely to prove value for money as a litigation culture increasingly takes hold in the UK. It was acknowledged that good doctors share knowledge of risks with their patients to promote patient buy-in and informed consent. Engineers in other industries emphasise the importance of training to cultivate attitudes where safety is always kept in mind. BPS raised the issue of medical students no longer being trained in a rigorously scientific manner how to prescribe, this was likely to eventually lead to more errors in doctor's surgeries. For patient safety and ease of use, medical equipment should be standardised, but this runs counter to manufacturers' desires to differentiate their products. Linguistic problems also arise, medical staff recruited from abroad may not have good English, and many patients also cannot speak English. The meeting concluded with a strong feeling that the NHS was generally doing a good job but that organisations like the National Patient Safety Agency needed to be supported in their efforts to improve safety systems.

Liz Bell

Scientists and the UK Parliament

Established in 2001 by The Royal Society as part of the Science in Society Programme, the MP/Scientist Pairing Scheme aims to build bridges between some of the best UK research workers and MPs. To date over 80 scientists and MPs have taken part.For more information visit http://www.royalsoc.ac.uk.

BIOSCIENCES FEDERATION

Another New Year has arrived. I hope that it brings you all the important things you seek and few of those that you do not.

From a political point of view I fear that the latter will not be true. The discussions about the future of the RAE have now reached a critical point. The momentum towards the abolition of peer review panels and the introduction of a metrics only based RAE continues. This change is supported strongly by many of your employers! External to Government, the main supporters of the metrics only approach are university vice chancellors and The Academy of Medical Sciences. All other 'academies', including The Royal Society, the Royal Society of Chemistry, the Institutes of Physics and Biology, and – of course – the Biosciences Federation are strongly opposed to the abolition of peer review panels. We want these panels maintained and we want them informed by robust metrics including those relating to output.

The main argument for change is to reduce costs – including those costs associated with time. We agree that strenuous efforts should be made to implement clear and substantial reductions in the bureaucracy associated with the RAE and believe that there should be serious discussion about how can this be achieved. A metrics only approach will achieve a cost reduction but this is not at all the right route to follow. Why do I write this?

First, because the BSF holds the view that it is potentially dangerous to rely on an algorithm for an activity as critically important as the RAE. We think it essential that there is some wise evaluation of the quality of the data fed into the formula.

Second, because the BSF thinks that a metrics based formulaic approach will disadvantage some areas of the biosciences. We are particularly concerned about those important disciplines where research is truly excellent but grant income is low and outputs may be relatively sporadic. Research in systematics is an example where these anxieties are relevant.

Third, and following from the previous point, the BSF thinks it likely that vice chancellors will inevitably move to support most those areas of the biosciences most suited to whatever algorithm that emerges. These areas will, of course, 'do well'.

And finally, and personally, because I have had too many computer generated letters from non-existent bank managers based on incorrect information or a 'mistake'. I have always managed to receive an apology and charges reimbursed. I doubt that you will get (m)any apologies out of the RAE!

What can you do about this situation? Well, of course, you can continue to support the BSF and I would welcome your ideas about how costs can be reduced effectively and peer review panels maintained. If you do decide to write to me, please make it brief and let me have your views by the 21 February. Some of you could also start an interesting discussion with your employer!

There are quite a few issues emerging that will have an effect on your professional lives. By the time that you read this, I will have met with a task force to discuss the BSF response to a paper published by the Research Councils' on peer review and our response will be on our web site. If you haven't seen the Research Councils' proposals, you might like to download them (www.rcuk.ac.uk/research/peer/efficiencypr.htm). I don't wish to prejudge our response to these proposals, but I am 100% confident that we will not be 100% supportive – and nor will you!

I am anticipating a busy year. However, I don't want all the activity to be reactive. A proactive position, taken at the right time, can often be more influential than 'fire fighting'. Ideally, I should like some of the issues where we should trigger debate to come from our member organisations. If you have thoughts about important matters to address in the next year or so please let us have them via your Council.

We are quite pleased by the number of 'hits' our jobs link page received during 2006. You may remember that this was a new initiative for us and is aimed to provide a resource for postdocs. I write 'quite pleased' because we are fully aware that all web sites can be improved. If you – or junior colleagues not members of the Society – have a thought about how improvements could be made please contact Dr Emma Southern (esouthern.bsf@physoc.org). In fact, please contact us about any bright ideas that you may have concerning the BSF. I don't promise to pursue them all, but I do promise to 'cherry pick' the very best for consideration!

Once again my best wishes for 2007.

Richard Dyer
Chief Executive Officer

Editor's note: Congratulations to Richard Dyer (below) on his OBE in the New Year Honours List for services to biology while working as Director of the Babraham Institute in Cambridge.

BSF database

The BSF will be creating a database of UK scientists who have high level expertise in policy work, who can be contacted when relevant expertise is needed. The database will be for BSF use and will not be made available to others. We are looking for Members of The Physiological Society who have top level experience of policy work that may be useful for the BSF. Examples of the experience that we seek might include membership of a Royal Commission, Chair of an RAE Panel or a Research Council Committee. If you are interested please contact Liz Bell (ebell@physoc.org) as soon as possible.

Ethics kills! Take scientific ethics too seriously and kiss your career goodbye

Scientific institutions are circulating guides on ethical behaviour. But before developing a conscience and becoming a 'grass', junior staff should think about the consequences very carefully.
Reading recent articles about fraud, a young scientist might be tempted to report any malpractice. But, if you would like your career to survive and your PhD to enable you to perform research and not land a tenure track position stacking shelves in a supermarket, don't breathe a word.

At an institution where I once worked a frightening incident occurred. It began innocently enough. A researcher was accused of fraud and 'persuaded' to resign. Then a sinister document called *On being a scientist, responsible conduct in research* landed on our desks. Published by the squeaky clean, United States National Academy of Sciences, it describes a range of unethical situations. It doesn't specifically mention cloning a range of domestic pets but it does mention fraud, and what to do about it. This usually involves going to see a responsible adult in a senior position who will sort things out in a professional manner. This was accompanied by a letter oozing patrician contempt suggesting that junior staff were moral neophytes who needed reminding of our ethical responsibilities. So, we just chucked it on our desks and forgot about it. When we did get round to reading it, we all came to one overwhelming conclusion: taking this document seriously will lead to a fast tenure track career path – straight to your local unemployment office.

Before 'grassing' or 'reporting an incident using the correct procedure', consider the consequences. Will you have a job to go to, will you be victimised, so you won but will you still have a lab to work in? Consider this – everything about scientific research is dependent on one thing: money.

Specifically the money your boss and institution can bring in. The expensive swivel chair that your boss parades in front of visitors. Their 'little perks'! Years ago I was naïve and looked at some air tickets brought with some grant money. I didn't realise that my boss's wife and 9 year old children were researchers who could present posters at an international conference. Then I realised it was in the West Indies. Even minor ego driven irrelevancies including consumables and staff need money. If the money disappears, you will be public enemy number one. Scandal will also damage the money-making potential of other labs in your institute. Nobody will like you, not your boss, your co-workers, management and especially your boss's 'associates'.

What about your boss's 'associates'?

Nobody likes a 'grass' – it's not the *Sopranos*, you won't be shot dead in the woods by a fat sociopath wearing white socks but your career will be. In any field there are usually about 10 people you could work for – our boss will know them all. Cause a scandal and every single one of them will be informed. Nobody will be silly enough to put anything in writing but without the support of the National Security Agency your boss's telephone conversations will be very hard for you to legally monitor. Every time you apply for a job your boss's 'associates' will be quietly reminded that you are untrustworthy, a source of trouble, and a 'nutter'. You will also acquire a number of bizarre and unpleasant sexual peccadilloes, especially if you are female. In a tribunal or court case every single one of your boss's' 'associates' will step into the witness box and perjure themselves senseless. Went to Oxford with Professor Johnny Fraudulent, 'diamond geezer', lovely rower, mainstay of my local Masonic lodge, research assistants making allegations should be strung up.

Can you afford the legal fees? Your institution will be spending a bottomless pot of other people's (tax payers) money on extremely expensive barristers, if you are lucky you might get a dodgy legal aid solicitor. Who is likely to lose? If you are really lucky, with an employment history as glowing as this you might get a job as a molecular biology advisor to the Chetchen government.

Can you prove it, and if you can you win but actually you lose

Proving wrong-doing is difficult, make an allegation and management's instincts will be to protect the money supply (i.e. your boss). Just suppose you can provide cast iron evidence of fraud, and management have been unable to hide the evidence or discredit you. You win. But your boss is discredited, he resigns or is sacked. Then your laboratory is closed

What do you do now? Try writing on your cv in the key skills section 'responsible for the molecular destruction of my last laboratory' or 'I uncovered fraud. My last boss is now living in the Cayman Islands under an assumed name, nobody will speak to me, three *Science* papers have been retracted and my last employers had to pay me a fortune in compensation. Oh, you can now read the entire thing on the front page of this weeks *Nature*.'

What should you do if you find out anything 'scientifically unethical'

As an insurance policy, collect as much written or computer evidence as you can. Make copies and secrete them where they cannot be recovered and 'lost'. You might think I am paranoid, but at one place I worked a disgruntled former employee tried to sue. A day later my boss smugly announced that he had been told to shred and delete anything incriminating by the head of the institution.

If you witness fraud say absolutely nothing, just quietly get out and get another job – it's cowardly but the repercussions of a conscience could be devastating. This is a cynical, dishonest but realistic view. If you are lucky enough to obtain hard evidence and you are threatened as a result of wrong-doing simply use it to cut a deal, get management to provide you with some good references or redundancy money and continue to pay your mortgage.

Derick Guillemot*

*Derick Guillemot is a *nom de plume*. Derick has worked in five labs in the last 20 years and has witnessed fraud in two. In both cases the culprit was the head of the lab. In one case 10 members of a lab all developed amnesia. Derick's current boss is entirely clean.

The trouble with medical journals

By Richard Smith
2006, Royal Society of Medicine Press. 292 pp.
£19.95
ISBN 1 85315 673 6

The trouble with medical journals is an authoritative, well written book based on the author`s many years of experience as Editor and Chief Executive of the *British Medical Journal* (*BMJ*). It covers the nature and values of medical journals, the processes and problems of publishing, relationships with the media and pharmaceutical companies, ethics and future scenarios for medical publishing. Reading the book made me realise how different medical journals are from the scientific journals published by The Society and that some of the problems the author raises are specific to the former. Medical journals are essentially magazines for doctors and, increasingly, for patients. They can, occasionally, publish articles that would be unlikely to pass peer review in a scientific journal worth its salt and this can have disturbing consequences. The author cites the paper by Wakefield (published in *The Lancet*) on autism and the MMR vaccine, as an example of how publication of a scientifically flawed study can have a major impact on public perception. However, he goes on to suggest that publication of articles containing little supportive evidence is appropriate for medical journals because they provoke debate. The problem is that the public and the media interpret what is published in a medical journal as always being scientifically sound!

Smith suggests that, although the original audience for medical journals was doctors and medical students, it is increasingly the public and the patient that are accessing these sources for medical information. He sees the role of medical journals as being educational, provoking debate and laying the background for political change where it relates to medicine and public health. Medical journals are in reality more journalistic than scientific (when was the last time you cited an article in a medical journal in a scientific manuscript?)

Despite his long career in medical publishing, Smith has a critical viewpoint on many of its aspects: 'All publication is theft!' He does not believe that peer review is of value, in its current form. He suggests it is an unproven system that involves bias, the potential for theft of ideas, undue influence of the author's name or institution on reviewers' decisions and a bias against negative results. One wonders whether he is really criticising the system or particular reviewers and editors. To my mind a scientific publication lives or dies by the quality and impartiality of its reviewers and editors. Encouragingly, Smith does make some useful suggestions to improve the peer review process, e.g. blinding of author name/institution, training for reviewers and their identification to the author.

The book deals in some detail with the relationship of medical journals with the pharmaceutical industry and the media. The former is regarded as an essentially unhealthy relationship. Most medical journals derive a significant part of their income from pharmaceutical advertising. This allows the journals to be provided free to many doctors. Doctors should not expect the pharmaceutical industry to support their education through provision of journals. However, this culture of interdependence, with both parties being willing participants and beneficiaries, will be hard to change. One wonders how many doctors would pay to receive medical journals? The dependency of medical journals on the pharmaceutical industry isn't just financial, they need to publish the latest clinical trials (supported by industry) to maintain their relevance and impact. It is unlikely that this relationship will be broken, but Smith suggests that it could be improved by making it more 'at arms length'. With respect to relations with the media, he provides a number of cautionary tales but concludes that interactions with the media are often valuable to the public and to the journals, providing that it does not debase the value of what the journal publishes. Press releases on high impact topics can be valuable as long as they are kept under control.

I found the sections of the book dealing with open access and the future of publishing particularly interesting as they are issues of direct relevance to Society publications. Smith outlines a number of pros and cons for the open access/author pays model:

For open access:
- greater dissemination of ideas generates more ideas
- the public (?) should not have to pay twice for research results
- the added value of peer review and distribution of publications is limited
- publishers make too much money from scientific publications
- academic credit for the quality of research will become uncoupled from publishing in 'high impact' journals.

Against open access:
- publishers do add value
- peer review maintains quality
- open access as a business model is untried and may collapse
- open access 'journals' may not survive and archival data will be lost
- many researchers cannot pay to have their research published and this model penalises high productivity labs and those in developing countries
- authors paying for publication encourages 'vanity publishing'.

Overall he comes down on the side of open access for research papers, but sees a changing role for medical and scientific journals. He suggests that the future role of journals will be to add analysis and interpretation to the research data. This analysis, review and interpretation will add value and should therefore justify subscription fees to journals. This is the reverse of the current approach for many scientific journals, which charge for access to research papers but make review and analysis articles available for free. Another interesting suggestion is that in an open access world, authors submitting manuscripts for review could pay for the peer review process

on a sliding scale. Thus, a minimum payment would be required for initial triage and payments would ramp up if the manuscript went for editorial review and would be the highest if the author requested detailed comments from the reviewers.

Smith concludes his book by considering various future scenarios:

1 No change to the current system (unlikely).
2 All research data open access and author pays for publication. Peer review is an open process. Magazines (journals ?) provide added value by providing comment and analysis and are funded by subscription and advertising. Scientific prowess will be assessed by the number of 'hits' on a research paper and by the practical benefits of the research (improved healthcare practise in the case of medical research).
3 All scientific information exchanged via the internet within specialist user groups. No role for publishers or journals (archiving would be a real problem in this scenario).
4 Large companies control and disseminate all medical information (a big brother scenario which also seems unlikely).

In addition to the topics I have discussed in this review, the book also has extensive sections on the ethical accountabilities of authors and of publishers.

This book is probably unique in the depth of analysis it provides into the world of medical publishing. It is also relevant in a number of areas to scientific journals. It doesn't make 'comfortable' reading for those involved in the publishing or editing of medical journals, but is challenging and thought provoking. Has the author written this book now that he has retired from the *BMJ* as a 'swansong' for medical journals? I don't think so. What is certain is that the publication and dissemination of medical and other scientific information is changing rapidly and we are just at the beginning of this process.

Mike Collis

Alcohol, tobacco and cancer

Edited by C H Cho and V Purohit. 2006. Karger (Basel). 312 pp. US$207.25 ISBN 3-8055-8107-6

Of the estimated seven million cancer deaths in 2001, 2.5 million or 35% were associated with potentially modifiable risk factors, prominent among which are alcohol and tobacco. Excessive alcohol consumption is associated with cancers of the mouth, pharynx, larynx, oesophagus, liver and colon. Smoking, in addition to causing cancers of the mouth, phaynx, larynx, trachea, bronchi and lungs, is also associated with cancers of the oesophagus, liver, stomach and bladder, among others. It's enough to stop you going out until the smoking ban is (finally) introduced, and then only to places serving mineral water and cranberry juice.

But for those with a strong constitution, this useful book brings together current thoughts on the mechanisms by which alcohol and tobacco initiate and promote cancer.

The first chapter gives a very brief overview of general mechanisms of carcinogenesis. This is followed by 11 chapters discussing the role of alcohol in cancer, including epidemiology, interactions between alcohol and tobacco, reactive oxygen radicals, pancreatitis and pancreatic cancer, breast cancer risk, and liver cancer. The final seven chapters discuss aspects of tobacco and cancer, including epidemiology, the role of nicotine (which is a cellular mutagen, carcinogen precursor and mitogen, as well as being addictive), and an approach to prevention based on developing a vaccine to nicotine. It's good to see the latter.

When as much money is being spent on research into primary and secondary prevention, as is currently spent on investigating the arcana of established (but incurable) disease, we'll know that real progress is being made.

John A Lee

Would you like a free book for your bookshelf?

The following recently published books are available in The Society's Publications Office and offered free to any readers who would like them. Please apply to lrimmer@physoc.org

- Programming the cerebral cortex (Stephen Lomber and Jos Eggermont)
- The nuclear envelope (Edited by D E Evans, C J Hutchison, J A Bryant)
- Wellcome Witnesses to Twentieth Century Medicine
  The MRC Applied Psychology Unit (Volume 16)
  The rhesus factor and disease prevention (Volume 22)
  Prenatal corticosteroids for reducing morbidity and mortality after preterm birth (Volume 25)
- Electric fields of the brain - the neurophysics of EEG (Paul L Nunez, Ramesh Srinivasah)
- Diversity in the neuronal machine - order and variability in interneuronal microcircuits (Ivan Soltesz)
- Brain development - normal processes and the effects of alcohol and nicotine (Edited by Michael W Miller)
- Neuroglycobiology (Edited by Minoru Fukuda, Urs Rutishauser, Ronald Schnaar)
- Long-term potentiation - enhancing neuroscience for 30 years (Tim Bliss, Graham Collingridge, Richard Morris)

Notices for the Summer 2007 issue of *Physiology News* should reach the Publications Office by 23 April. Please send contributions to lrimmer@physoc.org

AMERICAN THORACIC SOCIETY

San Francisco
18–23 May
International Conference for clinicians and basic science researchers specialising in various areas of pulmonary, critical care and sleep medicine.
http://www.thoracic.org

TRAVEL GRANTS

New travel grant deadlines for 2007 are now available at
http://www.physoc.org/grants

SOCIETY FOR ENDOCRINOLOGY

An essay-writing competition for undergraduates, with a first prize of £1,000 and two runner-up prizes of £250 each (deadline 23 March)
http://www.endocrinology.org

For news updates visit our online noticeboard at
http://www.physoc.org/news

SOCIETY MEETINGS/INTERNATIONAL WORKSHOPS

Krakow, Poland
9–12 May 2007
International Workshop *Endothelium: the determinants of cardiovascular health or disease*

Glasgow, Scotland, UK – Life Sciences 2007
8–12 July 2007
Joint Meeting of The Physiological Society, Biochemical Society and British Pharmacological Society (see details, below). Honorary Member Denis Noble (University of Oxford) will give the Paton Lecture

Manchester, UK
5–6 September 2007
Focused Meeting *Cardiac electrophysiology*: *with a special celebration of the centenary of the discovery of the sinoatrial and atrioventricular nodes*

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

Lviv, Ukraine
18–23 September 2007
International Workshop *Molecular physiology of membrane transport and cellular signalling*

Bristol, UK
17–18 December 2007
Focused Meeting *Renal cortex: physiological basis of glomerular and tubular diseases*

Cambridge, UK
14–16 July 2008
Main Annual Meeting

http://www.physoc.org/meetings (for Meetings)
http://www.physoc.org/international (for International Workshops)