PHYSIOLOGYNEWS

spring 2006 | number 62

Meetings

Manchester
Portugal
Brazil
Beijing, China

Also featuring:

A clinical scientist's week
Physiology in the extreme
Letter from Korea
An only transporter is a lonely transporter
Dying for a good night's sleep

A publication of The Physiological Society

Representatives of The Physiological Society and the Chinese Association of Physiological Societies meet to discuss a joint scientific meeting in Beijing, China in 2008 (see related article on p. 11). From the left: Prem Kumar (Meetings Secretary elect), Bridget Lumb (Meetings Secretary), Xiao-min Wang (Secretary General of the Chinese Association of Physiological Sciences), Giovanni Mann (Chairman of the Executive Committee), Tai Yao (President of the Chinese Association of Physiological Sciences) and David Eisner (International Secretary).

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

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Cover photos

Clockwise from top left: caiman, capabari, iguana and a group of caiman. From Ramage A, Taylor T & Lovick TA. Physiology in Brazil. pp. 7-10.

PHYSIOLOGYNEWS

Action points

Grants

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

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

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Physiology News

Deadlines

Letters and articles and all other contributions for inclusion in the Summer 2006 issue, No. 63, should reach the Publications Office (lrimmer@physoc.org) by 21 April 2006. Short news items are encouraged and can usually be included as late copy if space permits.

Suggestions for articles

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

Physiology News Online

Physiology News is now available on the Society's web site: http://www.physoc.org.

Guidelines for contributors

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

Format of articles

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

Length of articles

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

Submission of articles

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

Illustrations and authors' photographs

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

References

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

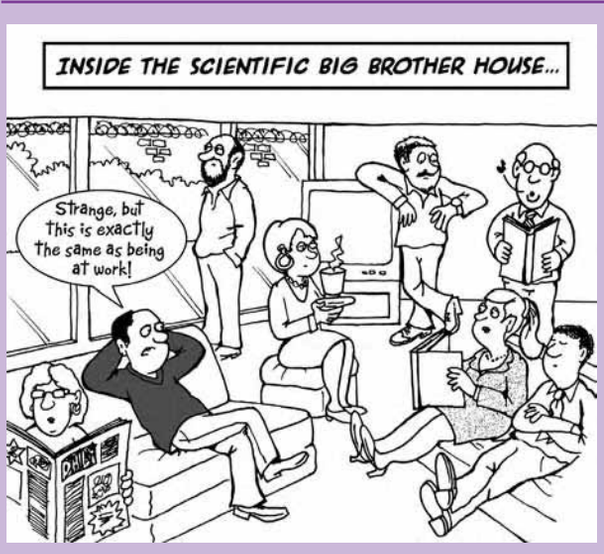
In this issue

Welcome to another issue of *Physiology News* – 56 pages again, incidentally, as we were once more spoilt for choice for content.

There is a short list of adjectives magazine editors like to use about their magazine and its content. 'Packed', 'exotic' and 'global' are three good ones. I like to think they all apply. I don't think I have seen another issue with quite such a breadth of features. Take the list of places where we have reports from, or about. Meeting previews for Portugal, Brazil and Beijing (not to mention Manchester), a letter from Korea, and Extreme Physiology from the Himalayas. The features have geographic range as well – four UK *vs* six non-UK, six Old World *vs* four New World, plus Australia for good measure. It all goes to emphasize, once again, the global nature of scientific endeavour.

Finally, and closer to home, we have a dozen pages this issue relating broadly to another topic important to scientists – education of the wider world, including but not limited to students, about science and scientific research. Scientists always need to keep in mind both the global and the local. I hope this issue gives you something to think about on both fronts.

Austin Elliott



I'm a leading scientist – get me out of here. Unbelievable! (p. 40)

Not complex, but vintage

In the last couple of years *The Journal of Physiology* has had the excellent idea of publishing occasional commentaries on landmark papers from its archives, together with web access to a PDF version of the original paper. I would like to suggest that similar commentaries should become more widespread, with the specific purpose of using older papers in undergraduate physiology teaching.

The American Physiological Society, which like our own Society is in the process of making all the back numbers of its journals – primarily the A*merican Journal of Physiology* – available online, has recently called for articles along just these lines for its journal devoted to physiology teaching, *Advances in Physiology Education* (Raff, 2005).

A major point of this idea is that papers from the older literature often use relatively straightforward methods that students can comprehend readily. This enables their reading of the paper to concentrate on following the logic of the experiments, their interpretation, and the deductive reasoning applied by the authors, rather than struggling to work out exactly what a *Cftr*^{tm1Unc}-TGN$^{(FABPCFTR)}$ mouse is, and how it differs from a common-or-garden *Cftr*^{tm1Unc} mouse. There is also a suggestion that the authors of yesteryear, perhaps because they had more time to contemplate their experimental interpretation and their writing, communicated what they had done rather more lucidly than is sometimes now the case. Finally, as I have commented before, I also suspect they were more likely than nowadays to discuss alternative interpretations to their preferred line.

So I think the suggestion has real promise. Helping students get to grips with the primary literature remains a stated aim of most undergraduate science degree courses, and large chunks of (especially) tutorial time are devoted to analysing and interpreting research papers. The modern trend in the UK seems to be to make this a part of the 2nd undergraduate year, the theory being that students will then be ready to apply these interpretative skills to the scientific papers that they read as part of final year dissertation or project work. I am sure I am not the only university teacher who has the impression that students often struggle to get past the Methods section of many papers analysed in this way. Given the tendency for papers to use multiple complex modern techniques, each with its own description in condensed jargon, this is hardly surprising.

Although it is often possible to interpret data without a detailed understanding of the methods used to derive it ('what do the Figures tell us?'), my subjective impression is that most students feel very insecure about doing this. The all-too-common result is a disconnect in their thinking between the experimental results and the methodology used to obtain them.

The end result is that the interpretation they derive from any paper is, in effect, likely to be no more and no less than what the paper's authors tell them it is, with little sense of whether this interpretation is truly supported by the data, or of whether other alternative interpretations could equally well apply. It is not clear to me what the gain is in this over just reading the abstract. While it is clearly assimilating literature, "interpreting" is stretching it, and we are hardly talking critical analysis.

Well, many academics will say, what do you expect? Off the record, many scientists will offer the opinion that it is not until some time during a PhD course that most learners these days begin to acquire the skills of reading papers critically, and then gradually. And these are typically students derived from the top 10-20% of the undergraduate first degree intake. We can all agree that full critical interpretation of scientific papers takes many years to learn, hence the fact that journal referees are typically principal investigator-level scientists.

This is all as may be, but I think that we as physiology teachers are not helping ourselves here. To give students a better chance of grasping the process of science, rather than just adding modern methods to their 'portfolio of the heard-about', we should start by leafing 30-plus years back into our journal collections. Papers of this vintage are far more likely to employ a single methodology, thus cutting the time needed to be spent on looking up 'hydropathy analysis' or 'SHG two-photon microscopy', or whatever. The controls will often be extensive, and extensively described, while the statistics will be simple. There is also an enormous choice of papers available, to enable us to pick ones that stand out as examples of lucid reasoning, or which have come to be regarded as classics. Once students have mastered critically reading papers of this type, they will have a firm foundation in scientific reasoning and a 'toolbox' of analytical skills to bring to more complex modern papers, with their proliferation of techno-methods.

So here is a challenge to any physiologists out there who feel they have witnessed the 'methodology overload' I describe in their interactions with their students. Go back to the earlier days of your discipline and find a *J Physiol* paper that does not contain five different techniques, but which makes careful observations, interprets them logically and clearly, and reaches a well-reasoned conclusion. Then ask yourself how that paper could be used as a teaching tool. And finally, write in and tell us about it. While I suspect *J Physiol* is unlikely to introduce an education section any time soon, *Physiology News* would be happy to oblige by bringing readers' selections for classic physiology *teaching* papers of this type to a wider audience. Together with our occasional feature on Ten Favourite Papers, I am hoping we can mine some real gold out of the rich seams of the past.

Austin Elliott

Reference

Raff H (2005). *Adv Physiol Educ* **29**, 138.

New university, new buildings, new staff

Welcome to the new look University of Manchester. Since The Physiological Society last visited in September 2003, the merger of the Victoria University of Manchester with UMIST has been finalised; bioscientists have moved into three new buildings (with a fourth about to be built); and an exciting group of young physiologists (and some not-so-young) has been appointed.

Merger officially took place in October 2004, with the creation of four Faculties. Life Sciences, the smallest, but most beautifully formed, of these Faculties, is where most physiologists are located, but there is a significant number in the Faculty of Medical and Human Sciences, most notably in the Division of Cardiovascular Studies.

Life Sciences was created by a merger of staff in the School of Biological Sciences (Victoria University), the Departments of Biomolecular Sciences and Optometry & Neuroscience (UMIST) and the Centre for the History of Science Technology and Medicine, most of whom are historians of biomedical science. In terms of physiology, the most obvious benefit is the coming together of neuroscientists from the two institutions.

The Faculty of Life Sciences acts as a single financial unit (School); but for administrative purposes is divided into three sections: Molecules to Cells (M2C), Cells to Tissues (C2T) and Tissues to Organisms (T2O), with most physiologists in T2O. Our Society President, Alan North, moved from Sheffield in 2004 to preside over the new Faculty as Dean and University Vice-President.

Most molecular and cellular bioscientists have moved into new buildings, namely the Michael Smith Building (opened December 2004) and the Manchester Interdisciplinary Biocentre (opened December 2005). A few physiologists work in the Michael Smith Building, but many will be

Above: The latest new bioscience building, which opened in February 2006, houses a Core Technology Facility on the ground and 1st floors, the Channels and Transporters Group on 2nd floor and the Cardiovascular Group on the 3rd floor.

Above: Mark Boyett, Professor of Cardiac Electrophysiology in the Cardiovascular Group, Faculty of Medical and Human Sciences.

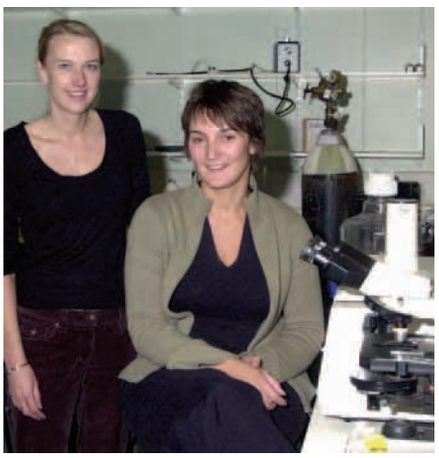
Above: Alison Gurney, Professor of Pharmacology, Faculty of Life Sciences.
Left: Some of the new Neuroscience staff (left to right): Denis Burdakov (brain circuits which control sleep and appetite), Ingo Schiessl (non-parametric analysis of functional brain imaging); Rasmus Petersen (coding tactile information in the CNS).
Below: New staff in the Channels and Transporters Group: back row (left to right) Jason Bruce (signalling cross-talk in non-excitable cells), Ian Fearon (oxygen sensing and the regulation of cell excitability), Donald Ward (extracellular Ca^{2+}-sensing receptors); front row Ita O'Kelly (left) (regulation and expression of membrane proteins) and Holly Shiels (cardiac physiology of ectotherms).

moving into a third new building (yet to be named) early in 2006, at which time construction of a fourth building to house the neuroscientists will begin.

Ignoring any barriers created by Faculties, Sections, Buildings (which are in any case very low), the strength of physiology in Manchester is generally focused on three overlapping areas: channels and transporters, cardiovascular physiology and neurophysiology. The two former groups are moving into adjacent floors of the third new building. During the past 3 years, all these areas have been strengthened by new appointments. In terms of professors, in addition to Alan North, we have gained Mark Boyett, who moved from Leeds in February 2005, and Alison Gurney from Strathclyde in January 2006. We have also appointed a dozen young physiology staff, many of whom are featured in the accompanying photographs.

The meeting in April is a Focused Meeting on the theme *Frontiers in epithelial transport*. This continues to be a significant area of research within the Channels and Transporters group, and has been strengthened by the recent appointment of Jason Bruce, Gavin Stewart and Donald Ward. The line-up of speakers for the meeting is first-rate – and, maintaining the tradition of Manchester meetings, we can assure you excellent hospitality.

Maynard Case
Faculty of Life Sciences, University of Manchester, UK



Top: Two more newcomers to the Channels and Transporters Group. Liz Fitzgerald (left) (molecular and cellular physiology of voltage-dependent Ca^{2+} channels) and Kath Hinchliffe (right) (inositol lipid function and regulation).
Above: Two of our four Research Council UK Fellows. Catherine Lawrence (left) (energy balance and neuronal function) and Natalie Gardiner (right) (sensory nerve regeneration).
Below: Epithelial physiologists studying channels, transporters and signalling in choroid plexus, gut, exocrine glands, kidney and placenta. From left to right: Maynard Case, Gavin Stewart, Peter Brown, Martin Steward, Donald Ward and Craig Smith.

Portugal Focused Meeting

An invitation to come to Portugal to talk, hear and discuss current research about cystic fibrosis, as well as enjoy the delights of the Algarve

This April in Portugal sees The Physiological Society venturing into what we believe represents an exciting new forum for Society-sponsored Focused Meetings, when the European Cystic Fibrosis Society (ECFS) joins forces with The Physiological Society to host an exciting conference on *New frontiers in the basic science of cystic fibrosis*. The meeting will take place from 19-23 April in Carvoeiro, once a small fishing village, but today still one of the most picturesque and flourishing seaside resorts on the south coast of the Algarve.

Our aim in organizing this unique venture was to broaden the scope of past basic cystic fibrosis (CF) science meetings (held since 2003), and help to foster new research interactions towards a better understanding of the pathogenesis of CF and of other related disorders. Of course we hope to maintain the important characteristics of past meetings by encouraging speakers to present their most recent unpublished results and ensuring a lively discussion of data and ideas at the forefront of research, all in an informal, co-operative atmosphere.

New frontiers in the basic science of cystic fibrosis
Symposia

- Lung physiology
- Calcium signalling
- SLC26 family of transporters
- Role of sodium channels in epithelial transport
- Post-genomics
- Biogenesis of membrane proteins and the ER quality control
- CK2 and epithelial biology
- The basic defect of CFTR in CF and how to correct it
- Epithelial cell biology, inflammation and pathogens

Above, left: Algar Seco-Carvoeiro
Above, right: Carvoeiro beach
Left: Tivoli-Almansor
Below: Carvoeiro grottes

The programme consists of nine symposia which will bring together 28 internationally recognized experts, covering key aspects of cystic fibrosis research and related themes, and will include a full day of physiological-based symposia that are at the cutting edge of current epithelial research (see list of topics on p. 5).

There will also be an opening keynote lecture by Alan Verkman (UCSF, USA) as well as several special interest group discussions in the evening. In addition, designated poster presentation sessions plus oral communications (chosen from submitted abstracts, in particular from young researchers) will run throughout the meeting. We expect to bring together the best of European and International experts, and strongly encourage post-graduate students engaged in cystic fibrosis and epithelial physiology research, to attend. Also of note during this conference, are presentations and discussions (open to all scientists) held by EuroCareCF, the recently EU-funded network of researchers aimed at coordinating research efforts in this area across Europe.

In addition to generous support from The Physiological Society and the ECFS, we would also like to thank the US Cystic Fibrosis Foundation (CFF) for their sponsorship, which has enabled the attendance of a considerable number of outstanding researchers from the US this year.

The conference will be open to a maximum of 120 scientists (invited guests and registrants). There will be no parallel sessions and we strongly encourage all participants to attend the full duration of the conference. The registration fee (1,000€ for regular registrants, 750€ for Physiological Society Members and 650€ for registrants under 30 years) covers hotel accommodation (4 nights), all catering, participation in the social functions and airport transfer on the pre-arranged shuttles. One day registration for Physiological Society Members only is also possible (225€).

It is thus with great pleasure that we invite you to attend this joint ECFS/Physiological Society 2006-Basic Science Conference. We welcome all scientists, not just from the field of CF, but also from a diverse range of related disciplines to an exciting conference of high scientific quality in the spirit of traditional Portuguese hospitality.

Looking forward to meeting you in Carvoeiro in the Spring.

Margarida D Amaral
Department of Chemistry and Biochemistry Faculty of Sciences, University of Lisboa, Portugal
Mike Gray
School of Biomedical Sciences, University of Newcastle upon Tyne, UK
Conference Chairpersons

Additional information (important deadlines, provisional programme, etc.) available online at:

http://www.europeancfconference.org/

Carvoeiro

Carvoeiro, probably born as a Moorish village, has a local history going back to mediaeval times as it was integrated into the kingdom of Portugal through King Afonso III who re-conquered the Algarve in the 13th century. We hope that, besides participating in a cutting-edge conference, you will be able to experience some of the flavour of the inspiring and graceful village of Carvoeiro and of its beautiful blue waters, as described below:

'On one of those late afternoons when we feel that spring is already arriving and we dream of summer, I found myself having a pleasant walk through the Carvoeiro streets. It was one of those aimless trips with no set schedule, where turning each corner is a new experience. There the panorama spreads out as if one were on a flight over the sea and the small cozy beach, an area of golden sand shaped like a shell, still practically deserted in the lukewarm March sun. On this day, the strong smell of the sea rises up over the cliff, and my gaze casts over the blue vastness but always returns to become fixed on the attractive group of white cottages that cling to the hill over the opposite side of the beach. Although most of the small cottages have been modified, they still remind one of the times when the daily routine of Carvoeiro's inhabitants was determined by the departure and arrival of the fishing boats. In those days the Carvoeiro beach was a place for hard work and not a cosmopolitan meeting and leisure place.'
[By: Maria José Pires. *Tribuna do Algarve*, 31July 1996]

Physiology in Brazil

In August this year, The Physiological Society holds its first joint meeting with the Brazilian Physiological Society. Brazil might seem remote to many, but for pharmacologists and physiologists it can be quite an attractive place as Thelma Lovick found out by talking to two Society Members who have active collaborations with Brazilian labs

Andy Ramage is Reader in Systems Pharmacology at University College London.

Thelma Lovick (TL) What took you to Brazil in the first place?

Andy Ramage (AR) It was one of those odd combinations of coincidences. It all started with a Brazilian, Henrique Futuro-Neto, doing a PhD in Birmingham in 1977 alongside Mike Gilbey. They were both doing their PhDs under John Coote and the two became good friends. Mike then moved to the then Royal Free Medical School (now UCL) and Henrique to the Departamento de Ciências Fisiológicas, Centro Biomêdico, Universidade Federal do Espìrito Santo in Vitória which is on the coast about 250 miles north of Rio. In 1988 they set up an exchange programme under the auspices of the British Council and CAPES and invited me and José Pires to join them. The uniting area of research was the role of central 5HT in cardiovascular regulation. I started in 1991 by going to the Departamento de Ciências Fisiológicas and carrying out experiments on the role of central 5-HT in control of the diving reflex. I enjoyed the time there and the work went well. In 1992 Mike decided to skip his trip as Gill, his wife, was pregnant. So, I went out to finish the work off (see Fig. 1) and it was during that trip that I became fully involved with Jussara whom I married.

Figure 1. Andy Ramage (centre) studying the effect of 5-HT_{1A} receptors in the control of the upper airway evoked reflex bradycardia in 1992 with José GP Pires (left) and Gilton (right), an MSc student.

TL So the Brazilian connection was the start of something good?

AR Oh yes, in more ways than one! I have been returning to Brazil for periods of collaborative work ever since. In December 1992 I was made a Professor Emérito of the Universidade Federal do Espìrito Santo. But now, with family ties there as well, it is also a chance to see my in-laws (!) and get my son to know his cousins. Figure 2 is a view of the beach from my proposed retirement home.

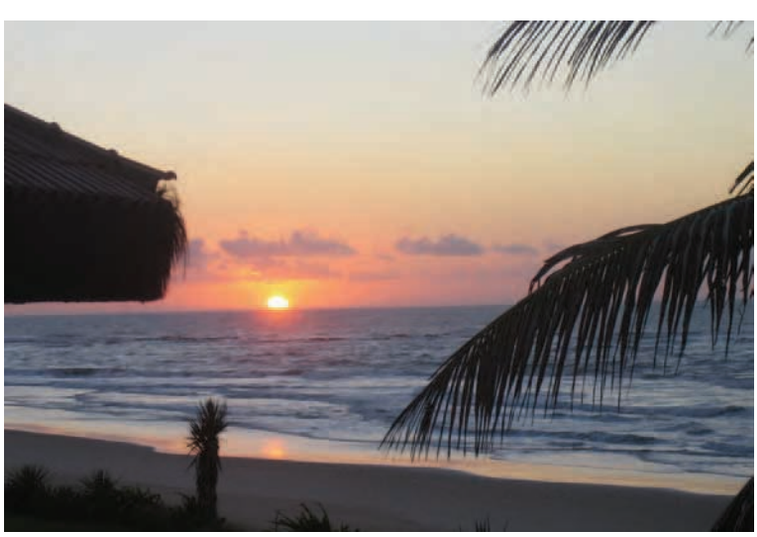


Figure 2. Life's a beach – the view from Andy's proposed retirement home in Brazil.

TL I suppose most people's perception of Brazil is carnival, rain forest, girl from Ipanema, delicious beef, nuts, that sort of thing; what's it really like being there?

AR When I first went there, it was a bit daunting. I did not speak any Portuguese and it is a fiendishly difficult language to get your head round. Things were OK in the lab because everyone wanted to practice their English on me, but English was not widely spoken outside, unlike nowadays. One thing that really took a bit of getting used to was the concept of hyperinflation, which was rampant at 200% a month when I first went. During an experiment people would be popping out to the bank to check their balance – and not just once a day!

TL And what about the science?

AR There is some very good stuff going on in the central autonomic area. I am continually impressed by the level of commitment and in the number of skills that the labs possess, especially regarding *in vivo* work. There are some

great young scientists but there is a log jam on the jobs front so there are more and more itinerant post docs touring the world. One great thing about working there, from a Brit's point of view, is that rats are free – well, the particular university I worked at supplies them free. It reminded me of those happy days in the UK, when the departmental budget could cover basic research needs. Also, Brazilian universities are not (yet!) run like a business, as they are becoming in the UK, and that is very refreshing. On the other hand, facilities were not that great 15 years ago, although the labs are now much better equipped and up to international standards. At the start I used to struggle through customs carrying stereotaxic frames and stuff like that. But there was always a genuine interest in what I was doing and an appreciation of why it was important. Now they think I am going to blow up the plane!

TL And what about the lifestyle?

AR The standard of living for academics is far higher than here in the UK. It took me a while to realise that when people invite you round and offer to cook you a meal, they mean that their cook will be doing it. The middle classes still have live-in servants.

Figure 3. Andy with Henrique A Futuro-Neto (left) and Benedito Machado after a lecture given at the Brazilian Physiology Society, Águas de Lindóia, Sao Paulo State on 25 August 2004. Centre front is Frederico, 8 years old, another product of the long term Brazilian collaboration.

TL Andy, what about the safety side of life – do they all live in gated communities?

AR Well safety is a problem. However, it depends what areas you go to and whether you look like a rich gringo; not a problem for UK academics! Two years ago Dan Kellett and I went to Ribeirão Preto to work with Benedito Machado (who is in the picture taken at the 2004 Brazilian Physiology Society Meeting) (Fig. 3). We arrived at the international airport in São Paulo, Guarulhos at 6.30 a.m. (the time most international flights arrive – from London it takes just under 12h) and caught a taxi to the bus station (Rodoviaria). A very nice bus, better than the airplane and a lot cheaper, took us to Ribeirão Preto, the place where the joint meeting will take place in August this year. The bus station seemed to be a fairly safe place. It took about 4h so we had a good sleep. Ribeirão Preto is very quiet and does not get a lot of tourists, so it's fairly cheap.

TL So would you recommend a trip to Brazil, to collaborate etc?

AR Yes and yes. I love Rio de Janeiro and Salvador – great places to visit and you only need a Hepatitis A vaccination. Keep your eyes open in Rio though, but the vista from Corcovado (with its statue of Christ) is fantastic. Ipanema is the better beach to stay. Working there is great, especially in my area of central autonomic research. However, collaborations usually occur depending on circumstances, the future experiments one is particularly interested in carrying out and also the nature of the collaborator. At present I want to learn how carry out *in vivo* voltammetry.

The science...

I am particularly interested in the role of central 5-HT pathways in the control of the autonomic nervous system. Brazil has experts in hypertension and cardiovascular reflexes and it is their expertise in whole animal experimentation, especially the use of conscious animals, that makes Brazilian physiology, for me, very exciting.

With Professors Futuro-Neto, Pires, Cabral & Mauad at the Universidade Federal do Espìrito Santo I have been investigating the role of central 5-HT receptors in the control of the sympathetic nervous system. We found recently that central 5-HT_2 receptors are involved in the control of vasopressin release and that vasopressin is essential for the development of DOCA-salt hypertension. We had hypothesised that this 5-HT system is involved in the central control of blood volume, thus we believed that by blocking it with mianserin (a non-selective 5-HT_2 receptor antagonist) we could prevent the development of DOCA-salt hypertension (Silva *et al*. (2005). *Eur J Pharmacol* **518**, 152). This system is probably also responsible for the hyponatraemia seen with selective serotonin reuptake inhibitors (SSRIs) in the treatment of depression. At present I am writing up a paper with Professors Cabral amd Mauad showing that activation of 5-HT_3 receptors in the NTS causes diuresis and selective inhibition of renal nerve activity in conscious rats. In another collaboration with Benedito Machado (University of São Paulo, Ribeirão Preto, where the joint meeting is to be held) we have been studying in conscious rats the baroreflex and chemoreflex. This led to a paper (Kellett *et al*. (2005). *Brain Res* **1054**, 61) that showed that 5-HT depletion causes attenuation of baroreceptor reflex gain in conscious rats.

Ted Taylor is Professor of Animal Physiology in the School of Biosciences at the University of Birmingham

Ted at work with Hamish Campbell.

Thelma Lovick (TL) Being a comparative physiologist must be one of the best excuses for travelling to exotic locations, but why Brazil?

Ted Taylor (TT) You have to go where the animals are, and Brazil is one of the best known biodiversity hotspots on the planet – it has possibly the most diverse flora and fauna of anywhere else in the world so it is **the** place for comparative physiology.

TL So how did you get to go there in the first place?

TT Well I first went to Brazil in 1995 to a meeting in Manaus. I'd had a Brazilian postdoc working with me in Birmingham who had recently returned home, so after the meeting I went to São Paolo to visit her. Then I came back in 1999 to work with Tobias Wang. Tobias is a research Professor at the University of Aarhus, Denmark but he has spent a lot of time in Brazil and speaks Portuguese. He introduced me to Augusto Abe at UNESP who has a wonderful animal holding facility with a huge collection of reptiles. There are captive breeding populations of three species of caiman, 2 species of turtle, tegu lizards, green iguanas and Burmese pythons. He is also able to obtain large numbers of rattlesnakes because of his links with the Butantan Institute in São Paulo, famous for its work on antisera against snake venom. However, our interest in these animals has nothing to do with them as biohazards. Both Tobias and I are cardiovascular physiologists and reptiles are really fascinating because they typically have incompletely divided circulations. They can shunt blood from the pulmonary to the systemic circulation and we are studying the control and possible functional roles of cardiac shunting. In 2005 I was joined by Hamish Campbell, a post-doc from Birmingham, and we used dataloggers to detect respiratory sinus arrhythmia in rattlesnakes.

TL Tell me about the lab environment. I imagine you don't send a requisition to the animal house a week in advance to order a caiman for Tuesday, say, like we have to do here with rats.

TT Right. We do have to catch our own animals. The caiman, which I'm doing a lot of work on at the moment, live in huge pens with concrete walls and a moat to simulate their natural environment. The breeding population lay their eggs in a sort of compost heap, which keeps the eggs warm and from this heap masses of tiny caiman hatch out. They are very attractive little animals but already very snappy and getting bitten is routine.

Ted Taylor (far left) with some of his collaborators in Brazil. From left: Jim Hicks (University of California, Irvine), Mogens Glass (USP Ribeirão Preto), Augusto Abe (UNESP), Tobias Wang (Aarhus) and Tadeu Rantin (UFSCar).

TL Isn't it a bit dangerous trying to work with some of these exotic species?

TT Yes, of course, but you just have to be careful. In fact reptiles are relatively slow compared to us as mammals, particularly when they are cool, first thing in the morning, which is when we are normally handling them in preparation for experiments.

TL What are the facilities like?

TT The animal holding facility is unbeatable – the best I've seen anywhere in the world. The animals are very well kept. There are good labs - loads of space. There are some very good Brazilian physiologists, mostly easy-going, friendly people. Standards are high too, and I find Southern Brazil a great place to work. The weather is hot of course – too hot for some – during the southern Summer (December through to March). There is tropical rain in the afternoon, making it hot and humid, so it can be quite tiring trying to work, but most labs I work in have air conditioning and in the evening we normally enjoy a cold beer.

We used to have to take much of our own equipment, things like blood flow meters, but now they have their own so we don't need to take so much. Funding for research is patchy across the country, most generous in southern Brazil and in particular São Paulo state via FAPESP. In 2004/5 I held a visiting Professorship for 6 months, sharing my time between UFSCar and UNESP. This was funded by FAPESP, which paid my travel and subsistence costs. We worked on

respiratory and cardiovascular coordination in fish and reptiles. There are also federal funds available from CNPq and active Brazilian researchers can obtain funds to travel abroad for collaborative work.

Brazilian academics work quite hard – teaching loads are high, although student numbers are not as high as is typical in the UK. The physiology teaching is fairly fundamental and broad based – students come in from a lower educational background than here. Many courses are taught in the evening, sometimes 9-11 at night. This is because some students from poor backgrounds do their whole degree at night as they have a day job to fund themselves. Although Brazil is a rapidly developing country, 40% of the Brazilian population is very poor. Academics are part of a small middle class, with a lifestyle reminiscent of the Edwardian era in England.

TL And what about life outside the lab? Where do you live?

TT Both Tobias and I enjoy rent-free accommodation for ourselves and associates provided by our friends and colleagues at UNESP, primarily Augusto Abe. Some visitors are placed in local hotels or rented apartments, which are cheap for anyone on a European or North American salary.

TL That brings me to the social scene. What's it like?

TT Unbeatable. In big cities like Rio or Salvador the beaches, scenery and nightlife are among the best in the world, but even where I work, in small towns in the interior, there are nice bars and restaurants serving good food, which is always fresh and very cheap. The cost of living is about 25% of that in UK. Brazilians are very sociable – a lot of fun to be with.

TL Do you speak Portugese ?

TT Not much, but I can order a beer and find my way around. I plan to take lessons this year. I can interact socially via my Brazilian friends so that we are able to get out to samba bars, drink and dance on our weekends off work.

TL Surely there must be some frustrations?

TT Well, for me there's the language barrier. Also, things take time, it's sometimes difficult to obtain some things like drugs for the lab, for example, especially in small towns, but communication is OK, just so long as you rely on email. So life is not quite so straightforward as here in the UK. You have to be a certain sort of person – you need to be fairly laid back. There can be problems with transporting equipment – you might get a swingeing customs 'duty' levied on new equipment or even get it impounded by customs in some obscure office somewhere – and it's a big country with a virtual absence of anything typically 'British' about it. It wouldn't suit everyone.

TL So far so fabulous. Have you bought your retirement home there yet?

TT I'm thinking about it. When I do finally retire from the day job in Birmingham, this September, I'm planning about a 50/50 split between the UK and Brazil. Brazil suits my personality – work hard, play hard (well fairly hard!). I have an open invitation to stay with friends whenever I go, so I'm pretty lucky.

In September 2005 Ted Taylor took a party of 16 undergraduates (some of whom are pictured below) from Birmingham to Brazil to study animal physiology. From the original 65 students who were keen to go, 16 were chosen on the basis of the standard of their academic performance. Each student needed to raise £1,000 and a further £10K was provided by the University of Birmingham.

Ted Taylor comments: They were a mixed group in terms of personality and background but all proved to be very able students. They worked extremely hard on a range of animal species, including terminally anaesthetised turtles, measuring blood flows etc. and chronically instrumented frogs, lizards and caiman, studying heart rate and blood pressure after pharmacological blockade. The level of animal experimentation was far in advance of anything the students had previously experienced and would have been impossible to sustain without the expertise of Tobias Wang and his two demonstrators, Nini and Marianne from the University of Aarhus. All experiments were closely supervised by one of us and followed the general ethical standards applied in the UK and Denmark, and according to the controls exerted in Brazil. We instructed the students to write up their experiments like a paper in a journal. Some may indeed prove worthy of publication.

The science ...

Our work in Sao Carlos centred on control of cardiorespiratory interactions in fish. At UNESP in Rio Claro we are making a comparative neuroanatomical study of the vagal motor column and doing physiological investigations of cardiac shunting, venous filling pressures and intrinsic vasomotion in the lung in reptiles including turtles, lizards, caiman and snakes.

Pharmacological approaches are being used to uncover of the classic roles of the autonomic nervous system in the cholinergic and adrenergic control of the cardiovascular system as well as bradykinin, neuropeptide G and histamine (Skovgaard *et al.* (2005); Galli *et al.* (2005a,b). Using data loggers to measure heart rate variability, we have recently identified respiratory sinus arrhythmia in the rattlesnake and caiman.

Galli LJ, Skovgaard N, Abe AS, Taylor EW, Conlon JM & Wang T (2005a). Cardiovascular actions of rattlesnake bradykinin ([Val1, Thr6]bradykinin) in the anaesthetised South American rattlesnake *Crotalus durissus terrificus*. *Am J Physiol* **288**, R456-R465.

Galli LJ, Skovgaard N, Abe AS, Taylor, EW & Wang T (2005b). The role of nitric oxide in the regulation of the systemic and pulmonary vasculature of the rattlesnake *Crotalus durissus terrificus*. *J comp Physiol*. **175**, 201-208.

Skovgaard N, Galli LJ, Taylor EW, Conlon JM & Wang T (2005). Haemodynamic effects of neuropeptide γ in the anaesthetised python, *Python regius*. *Regulatory Peptides*, **128**, 15-26.

Brazilian acronyms

CNPq Conselho Nacional de Pesquisa

FAPESP Fundação de Amparo à Pesquisa do Estado de São Paulo

UFSCar Universidade Federal de São Carlos (a campus of a federal university)

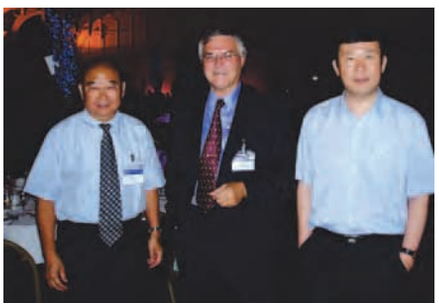
UNESP Universidade Estadual Paulista

Joint Meeting of the Chinese Association of Physiological Sciences and The Physiological Society in Beijing, China in 2008

In a recent article (*Physiology News* **59**, 10), David Eisner highlighted that the International Committee of our Society is committed to building closer links with China. This process began with a visit to China by Giovanni Mann in 2004. Our Executive subsequently met with Professor Tai Yao (President) and Professor Xiao-min Wang (Secretary General) of the Chinese Association of Physiological Sciences at the IUPS meeting in San Diego in 2005, and we agreed to hold a joint scientific meeting in Beijing, China in the autumn of 2008.

We then invited Tai Yao and Xiao-min Wang to the FEPS meeting in Bristol in July 2005 and to a planning meeting chaired by David Eisner (International Secretary) and attended by Bridget Lumb (Meetings Secretary), Prem Kumar (Meetings Secretary elect) and Giovanni Mann (Chairman of the Executive Committee). Xiao-min Wang kindly agreed to explore potential venues/costs for holding the joint meeting in Beijing and has recently informed us that the meeting would need to be held after 10 October 2008. In Bristol, we also discussed the possibility of inviting the American Physiological Society to sponsor a designated symposium at this joint meeting, and David Eisner will be liaising with Marty Franks, their Chief Executive.

Coincidently, the Society for Free Radical Research International (SFRR) will be holding its 2008 meeting in Beijing, China. The Physiological Society has previously sponsored research symposia at SFRR meetings in May 2004 in Buenos Aires, Argentina (*Physiology News* **57**, 31) and in July 2005 in Leicester, UK, and it may be possible to schedule our joint meeting in Beijing back-to-back with the SFRR International meeting. As a member of SFRR, Giovanni Mann has asked their Council to consider co-sponsoring a symposium on the role of reactive oxygen radicals in cell signalling. Professor Angelo Azzi (Secretary General of SFRR-International) replied that 'a joint symposium between the Physiological Societies and SFRR-International will certainly be welcome'. The dates for their XIV Biennial Meeting of the SFRR-International in Beijing are 15-19 October 2008. Giovanni Mann hopes to further discuss a joint symposium with their Council during the forthcoming SFRR-International meeting in Davos, Switzerland from 15-19 August 2006 (for further details see: http://www.sfrr-congress.org/).



Prior to the FEPS meeting in Bristol, Tai Yao, Xiao-min Wang and Giovanni Mann visited Windsor and on the way back to London with Richard Siow spent a pleasant afternoon in Bath sampling English tea and coffee! The photographs highlight the FEPS meeting in Bristol and visits to Windsor and Bath.

We are delighted that The Society will be strengthening its research/academic links with colleagues in China, and it was a personal pleasure to have welcomed Tai Yao and Xiao-min Wang to the UK on behalf of The Physiological Society. We look forward to an exciting scientific meeting in Beijing in 2008!

Giovanni Mann
Chairman of The Executive Committee

David Eisner
International Secretary

From the top:
Tai Yao (President of the Chinese Association of Physiological Sciences) with *Experimental Physiology* Chair John Coote.

Tai Yao, Xiao-min Wang (Secretary General of the Chinese Association), and Society President Alan North.

Tai Yao, Xiao-min Wang and Giovanni Mann in New Hunt's House Library, King's College London.

Tai Yao and Giovanni Mann outside the gates of Windsor Castle.

Richard Siow (KCL) with Xiao-min Wang in Bath

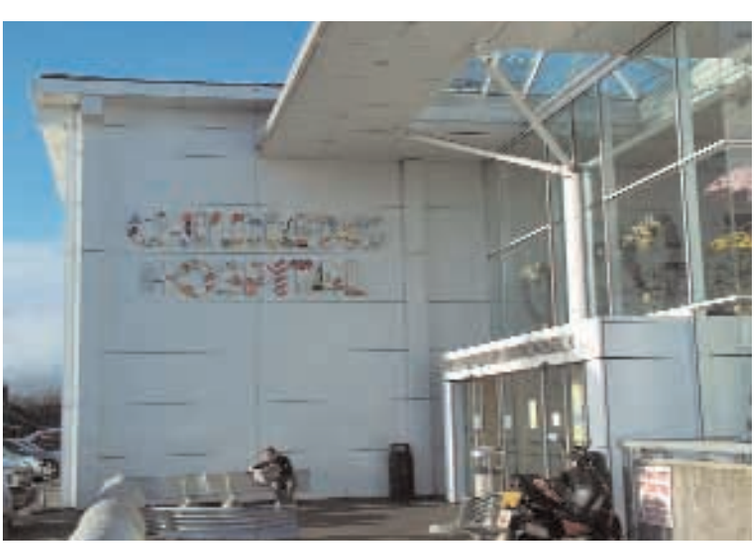
A week in the life of a clinical scientist

Case conferences, ward rounds, mass spectrometry and unspeakable things in jars are all in a week's work for Tim Lang

When Austin Elliott first asked me to write about my work as a clinical scientist – more accurately, when he cornered me at the wedding of a mutual friend of ours and two drinks past the point of remembering to say I was too busy – it had been 5 years since I had finished my PhD. In the intervening years I trained as a clinical scientist, and am currently in a Principal Clinical Biochemist post in the Regional Paediatric Biochemistry Laboratory in Belfast. This lab is the regional centre for the investigation of inborn errors of metabolism and has strong links with the Royal Belfast Hospital for Sick Children and Royal Maternity Hospital. It was here that Nina Carson and Desmond Neill described the first case of homocystinuria in1962.

So what does a clinical biochemist actually do? Well, some days we do 'frantic'. I definitely never thought, when I was a graduate student, that one day I would be involved in some of the diagnostic storylines you see in dramas like ER. There are times when the pressure is on to deliver an urgent result, similar to the pressures of submitting a grant application with an ever more rapidly looming deadline. Delivering a result is not just a matter of giving the clinicians a number. Clinical scientists are involved in a number of processes from when the patient presents to the doctor to when the test results are reported. This is especially true in paediatric biochemistry. More often than not we can find ourselves being sought out for an opinion early on in a particularly difficult case or emergency, and having an input into how the patient is investigated.

Once, for instance, I had just sat down in my office when there was a bang on the glass – there, stationed outside, were the consultant paediatric neurologist and both specialist registrars, wanting to talk about an acutely urgent case. Two registrars and a consultant definitely screams 'triple urgent' – people who know medicine will tell you that outside of a ward round or a departmental meeting it is nearly impossible to get this many doctors this senior in one place at one time! In this particular case the patient had presented with severe encephalopathy, and the biochemical investigations needed to be performed urgently to provide the diagnosis that would aid with management and prevent irreversible brain damage. Rarely does a child present with textbook symptoms, so it is up to clinical scientists to work in partnership with the clinicians to facilitate the investigations. It is in this sort of case where you still feel like an investigator.



Tim Lang (above)

Royal Belfast Hospital for Sick Children (left)

Less 'ER-like', of course, are the times when you are presented with dubious looking samples in jars and tubes, ranging from the particularly offensive faecal sample (sadly a hazard of the job) to various strangely-coloured urines! I remember one particularly odd request from A&E relating to an unconscious patient with suspected alcohol poisoning. The patient had been working in the garden shed and had consumed an amount of mysterious lime coloured liquid, which Casualty thought may have contained anti-freeze. Luckily it turned out that it was only lime cordial.

Clinical liaison/co-operation between the clinical scientists and clinicians is something that is essential and really is actively encouraged. This type of relationship is probably not seen between academic scientists and physicians, as their joint subject of investigation is less likely to be actual patients with symptoms, and more likely to be bits of data, or other pieces of a scientific jigsaw. However, it is important to remember that the time-frames are very different. It may take years of research to answer a particular question (if you're lucky!), whereas in the clinical situation it might be hours, or days, or sometimes weeks before a firm diagnosis is reached. Like everyone else, I had heard the 'war stories' about friction between the different professions in hospitals, but my personal experience has been quite the opposite. In fact, I would say the most pleasant surprise for me, working as a clinical scientist in paediatrics, has been the healthy partnerships that are established between the different professional groups.

So what do I actually do in a typical week? This is harder to answer than

you might think as, due to the specialist nature of paediatrics, no day or week is ever the same. But there are a few fixed points.

One day a week I participate in the duty biochemist rota for clinical validation/authorisation of tests performed in clinical biochemistry, so I am on-call to offer advice or interpretation of results for clinicians and other healthcare professionals. Being on duty can be very busy at times and you soon learn how to prioritise tasks. It can be quite a challenge, especially when you are trying to locate a doctor who is not answering their bleep (yes, that bit is true). You are not just there to deal with clinical problems, as analysers in the hospital biochemistry lab are just as prone to failure as patch clamp rigs, or imaging systems, or centrifuges. Unfortunately, when something breaks you can't just end the experiments for the day and go to the pub (not that I ever did that as a PhD student, just in case my ex-supervisor is reading this). You will have to try to solve the problem, or make alternative provision, as most hospital labs provide a 24 hr service.

On Tuesday mornings I have the opportunity to attend the weekly special care baby unit (SCBU) ward round, where cases of the recent and current admissions are discussed in the presence of all those involved in their management, from clinicians to nurses to biochemists. Very occasionally there may be a case where a neonate has presented at birth with a suspected metabolic disease of unknown cause. When this happens I offer advice and liaise with the clinicians in order to pinpoint the suspected metabolic condition.

One thing that appeals to me about my job is the opportunities available to participate in research without next year's grant application hanging on the outcome. Most of the research relates to the development of the service, and there are links in most hospitals for supporting clinical research and trials. At the moment some of my time is spent preparing and developing an assay for the measurement of acyl-carnitines using tandem mass spectrometry, which we hope will improve the investigation of patients with suspected fatty acid oxidation defects. Just as in The Physiological Society, we are expected to present our finding and interesting cases for peer review. The Association of Clinical Biochemistry (www.acb.org.uk) organises a number of regional and national scientific meetings, where junior members are especially encouraged to do oral and poster presentations. This week I am spending some time preparing a clinical case history for presentation at a national meeting on inborn errors of metabolism – a bit like a Phys Soc communication. So there are the usual PowerPoint slides to be prepared, and figures to check for errors.

Whilst preparing the talk I get a call from a clinician in a local district general neonatal ward requesting advice on the possible diagnosis of a sick baby who has presented with recurrent episodes of hypoglycaemia. After taking a clinical history of the baby I am able to suggest the appropriate biochemical investigations to be performed and discuss a possible differential diagnosis. The following day we receive specimens, which we analyse urgently. Normally before the results are released to the clinicians I review them and, if necessary, add some interpretative comment or suggest further investigations. In this case I contact the requesting doctors and discuss the results with them in light of any change in the child's condition.

On a Friday morning I attend the multidisciplinary paediatric ward meeting in the Children's Hospital. Here difficult cases are discussed and any outstanding results followed up. I normally come back with a number of cases to follow up or read up on. As it is such a wide topic you can never know everything and there are always developments occurring in the field. The current reference textbook for

Careers in clinical science

Career entry is through the NHS Clinical Scientist Training scheme, which recruits a number of scientists into a variety of disciplines every year through a process similar to the annual graduate milk round. Trainees are recruited to regional centres, normally large teaching hospitals, where they spend 2 – 4 years in training, depending upon the discipline.

Training involves:
- on-the-job training in the laboratory
- a taught MSc course
- opportunities to attend other training events
- a 3-6 month secondment to a district general hospital.

During the early part of your career you are expected to be mobile - similar to being a post-doc, but with the security of a permanent, or at least a 3-5 year, post. However compared with post-doctoral work there is a structured career path, which can eventually lead to consultant clinical scientist status, equivalent to a medical consultant. Progression through the path is dependent upon experience and, for more senior posts, obtaining membership of the Royal College of Pathologists (MRCPath) through examination. This is the only Royal Medical College to admit non-physicians to its ranks.

Things to do if interested:
- visit a local laboratory or department
- speak to a clinical scientist
- work shadowing/experience in a hospital lab
- contact the appropriate professional body

Useful web sites:
http://www.nhscareers.nhs.uk (NHS Careers)
http://www.nhsclinicalscientists.info (NHS Clinical Scientists Recruitment Service)
http://www.acb.org.uk (Association of Clinical Biochemistry)

The Regional Paediatric Biochemistry Laboratory in Belfast (left)

Royal Victoria Hospital, Belfast (below)

inborn errors is composed of four very heavy volumes. Definitely not something that would fit in the pocket of your white coat!

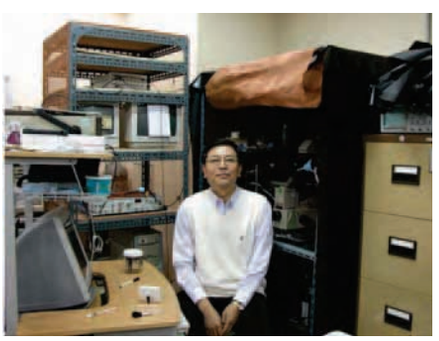
Friday afternoons are always quite busy so sadly there is no chance of slipping off early to the local pub – almost makes me nostalgic for my PhD student days. There will be results to be reported to clinicians before the weekend, and batches of tests to authorise. Friday afternoon is also normally when you get the phone call from a clinician wanting a test performed urgently, typically at 4.30 p.m. when you are finishing off an assay and looking forward to going home. Depending on the clinical history of the case you have to decide whether it can be assayed. A big consideration is whether the patient's management would change depending upon the result. There is also the question of whether the right staff are available to analyse it over the weekend.

Last minute crises sorted, I head for home and a different kind of 'busy working environment' … those with young children will know exactly what I mean! Anyway, I hope this has given you a snapshot of a week in the life of a clinical scientist. I have found my 6 years in the career very rewarding and varied – every day really is different and challenging. PhD students and postdocs who don't think a career in academic science is for them, but would still like to use their scientific knowledge hands-on, could do a lot worse. If I have convinced any of you, the box on p. 13 gives some info on how to look into careers in clinical science.

Tim Lang
Regional Paediatric Biochemistry Laboratory, Belfast, N Ireland

Letter from ... Korea

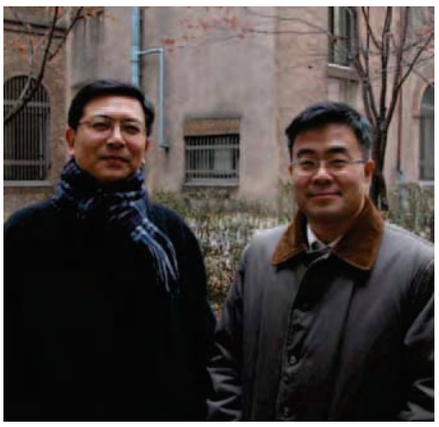
'Land of morning calm' was the name by which we previously called our country. Nowadays, however, it is hard to find a 'calm' place in Korea. Since the Korea-Japan World Cup games in 2002 a more popular, and probably more exact, portrayal would be 'dynamic Korea'. Dynamic and rapid changes have occurred, not only in the modern industry, but also in physiology research in Korea. Most of the changes are progressive and, every year, state-of-the-art techniques are introduced to the field. In addition, one of the influential slogans from the Korean Ministry of Science & Technology is the development of so-called Fusion Technology (like Biotechnology and Information Technology, BIT). Infiltration of ideas, as well as technology from other fields of science, has greatly changed the themes and titles of presentations at the Annual Meeting of the Korean Physiological Society (KPS). Although awkward at first, the progressive effects of such changes will become obvious in the near future. The most popular food in Korea is 'Bibimbap', a steamed rice with assorted mixtures of vegetable, minced beef, and hot sauces. (I have to say that we really mix them well with a spoon just before we eat it. A spoon of sesame oil is an important ingredient). Hopefully, the KPS can be the large 'bowl' for a Bibimbap of life science.



Insuk So in his smooth muscle research laboratory.

Here, we would like to briefly look back upon the recent history of the Physiology Department at Seoul National University. Our Department is located on University Road in central Seoul. For the last 30 years, electrophysiology of excitable tissue

has been the main theme of our research. We started in 1976 by recording action potentials from frog atrial muscle with very primitive hand-made equipment. Between 1978 and 1985, two-electrode voltage clamp techniques and patch clamp methods were introduced for the study of cardiac muscles, smooth muscles and neuronal cells. Through this period, the support from Denis Noble (Oxford) Hiroshi Irisawa (Okazaki) was a great advantages to us. The introduction of patch clamp techniques to Korean physiologists was a very successful story and it became the most popular research technology for the last 20 years. Combined with fluorescence imaging technique, confocal microscopy and molecular biological methods, we are widening our research focus into various tissues and organs. At present, the major research in our Department includes response of cardiovascular sensing mechanisms for hypoxia and mechanical stress, learning and memory mechanisms of neuronal system, molecular nature of pain, pacemaking activity in gastrointestinal tract, exocytosis and the role of calcium in presynaptic terminals. In most of those studies, the physiological roles of ion channels have been focused at various levels.



Top, left: Insuk So (left) and Sung Joon Kim in the old quadrangle building of Seoul National University College of Medicine.

Top, right: Sung Joon Kim on top of the mountain in Moo-ju ski resort where the 2005 KPS meeting was held on October 20.

Above: Annual winter symposium for ion channel research in Korea. It is usually held in a mountain resort and, after the symposium, climbing is our tradition. This photo was taken from an old Buddhist temple in Jiri mountain. From left to right, Chae-Hun Rheem (Ulsan Uniersity), Myung-Kyu Park (Sungkyunkwan University), Hyo-Won Bang (Chung-Ang University), Min-Goo Lee (Yonsei University), Sung-Joon Kim (Seoul National University), and Tong-Mook Kang (Sungkyunkwan University).

With the development of the Korean economy, government support has also increased. Approximately 5% of the national budget was allocated to research and development projects. Although the present government places too much emphasis on the application of research, the total allocation is much increased. In general, the number of scientists who work for life science is increasing, especially in the area of molecular biology. The rate of expansion in physiology is rather slower than that of other fields of life sciences. Around 400 physiologists attended the KPS Annual Meeting last October. Traditionally, the main topics are ion channels, molecular physiology, system physiology and neurophysiology. In 1995, a joint symposium with The Physiological Society was held to celebrate the 50th Anniversary of the KPS. Around 35 physiologists from the UK attended this meeting to present their work, and lively discussions took place with Korean physiologists. The main themes of the Joint Meeting were cardiovascular ion channels, epithelial and membrane transport and neurophysiology.

2006 has a very special meaning for our Society. KPS hosts the 6th Congress of the Federation of Asian and Oceanian Physiological Societies (FAOPS, www.faops2006.org) on 15-18 October. This meeting consists of three plenary lectures, eight special lectures and 22 symposia. This Congress was approved at the 4th FAOPS meeting in Brisbane, Australia in 1998. In fact, hosting an international meeting like FAOPS is a first experience for KPS, and all the members and the Council of KPS are trying their best to host the guest scientists and speakers. Professor Ki Whan Kim (Seoul National University) was nominated as a chairman of The Organizing Committee of the 6th FAOPS meeting. With the Organizing Committee, KPS is doing their best to ensure a successful meeting. Please try to visit Korea at this time and enjoy the 6th FAOPS meeting. 'Kam-Sa-Ham-Ni-Da' (Thank you very much!)

Insuk So
Sung Joon Kim
Department of Physiology, Seoul National University College of Medicine, Seoul. Korea

Physiology in the extreme

Thelma Lovick talked to another intrepid physiologist who takes his science into the extreme. Below, John Coote, Professor Emeritus in the Division of Neuroscience at the University of Birmingham, shares some of his experiences of doing physiology in the extreme environment encountered at high altitude

Thelma Lovick (TL) I understand you've worked in the Peruvian Andes as well as in Chile, the Italian and Swiss Alps, Karakoram in N Pakistan and in Nepal in the Everest region and Himulchuli. How did you get started on all this?

John Coote (JC) Well as you probably know, I used to be quite a keen climber. When I first went to East Africa to climb the north face of Mt Kenya, I experienced severe headaches and nausea and it took me several days to recover. Within our group, though, some weren't affected, and I began to wonder about the reasons for this individual variability in the ability to adapt to low pO_2. There are also more prosaic reasons for needing to understand our reactions to low pO_2. The military is obviously very interested in ways to keep the troops in peak condition if they are flying them in over long distances to drop them into a high altitude combat zone. Skiers, too, can be badly affected by low pO_2.

TL So why do you need to take your lab to the mountain when there are perfectly good altitude labs around the world where you can live and experiment at low pO_2?

JC I thought you'd ask me that! My interest is in the response of lowlanders to long periods at altitude and the best way to simulate this is to actually be there. Also, altitude chambers aren't that comfortable to be in. And compared to the mountains the view is terrible!

TL Tell me how you set up one of these expeditions.

JC There's months of planning involved. Inevitably, when you go to remote areas with poor access, you have to take your whole lab in a portable form. You have to take spares and be prepared to be quite resourceful in terms of mending equipment in the field.

John Coote pedals up Everest

TL How do you transport all this stuff? Presumably there are no roads.

JC Well, you helicopter everything in to give you a start. Then it goes on to pack animals or on to the backs of porters. Always when going above 18,000ft you have to use local porters. In fact, portering provides quite a boost to the local economy in many areas and there are often queues of guys waiting to be selected.

TL Let's take one of your trips to Everest. Is it really the mess we hear about?

JC I'm afraid it was, although attempts are now being made to clean it up. When I was last there, which is now 10 years ago, the route in was littered with the debris left by Westerners.

Extract from John Coote's diary

July 12 (18,000 ft)

4.30 a.m. Wake after good night's sleep to see it's snowing heavily. Temp outside minus 30 degrees. I feel warm and cosy in sleeping bag. I have all my outside clothes on, 2 pr socks, woollen long-johns and salopettes, wool vest, shirt and pullover, balaclava and hood of bag pulled tight to leave small breathing hole through which 13 leads connected to Medilog recorder and Bioximeter pass.

Generator worked throughout night, no doubt thanks to Pete and Neil keeping the fuel supply going every 2 hrs. So biox worked all night. Alveolar oxygen now at 52 mmHg. It snowed all day, about 18 inches, tents completely submerged 2 collapsed. Clear some of the snow but not much else done today.

TL And are you guilty of adding to that?

JC We do our best to bring everything out with us, but I must confess there are occasionally things that fall down crevices when we're at high altitudes.

TL Tell me about a typical day.

JC We live in tents in the snow and the day starts when one of the porters brings you hot sweet tea to get you going. Then you get out of your sleeping bag, have something to eat and set to work.

The days are very organised – everyone has a designated task and nobody is idle. We may all have to attend the medical tent to be weighed, measure body fat, heart rate, blood pressure, give saliva, blood samples, etc. If you're doing a sleep study your electrodes for EEG, ECG and ventilation will need removing or replacing along with your Medilog recorder. In an exercise study we take along a bicycle ergometer and test people at different workloads. The bike is heavily used and takes a lot of punishment. We often have to use it outside so it's very unpleasant if you're the minder of the bike!

The scientific question

As we fall asleep our brain responds less to the outside world, yet it does not switch off. The sleeping, but active, brain actually requires increased amounts of oxygen compared to the resting awake brain. To supply this, blood flow increases. Studies in sleeping animals suggest that the blood flow changes are finely tuned by the arterial chemoreceptors, which are one of the few afferent inputs that maintain a strong influence on brain activity during sleep. At sea level, where the blood is fully saturated with oxygen, the blood flow increase in sleep is sufficient to supply the needs of the brain even though ventilation is slightly decreased. However, at high altitude the barometric pressure can be low enough to seriously decrease SaO_2 and an alteration in oxygen delivery to the brain during sleep can severely affect brain activity. It is not surprising, therefore, that hypoxic insomnia is a common complaint amongst trekkers, skiers and mountaineers sojourning above 10,000 ft. So what are the physiological changes in visitors to high altitude and, even more interesting, how have residents at high altitude adapted? These are questions that have kept drawing me back to the mountains.

TL What about meals?

JC Lunch and tea breaks are organised by the porters and Sherpas. But you don't eat a lot. You're busy, it's cold, you have no appetite and it's actually quite hard work to make the effort to eat. The whole environment is not exactly conducive to eating and the food is mainly dried stuff. Above 18,000 ft we exist mainly on tea, porridge, chapatis, jam and reconstituted soup and stews – it's not a great culinary experience. You need about 3000 Kcal per day, but I don't usually have more than about 1500 Kcal so consequently I lose around a stone or more over a month.

When you stop working you just want to get into your sleeping bag to keep warm. You go back to your two-man tent once you've finished your work and maybe chat to your companion for a bit before the final meal of the day, or you just have a snooze. This can actually be quite worrying if the other person remains awake at this time because at altitude you go into periodic breathing and you may stop for quite long periods of time. There have been incidents when non-medical scientists have panicked because they thought their partner had died!

TL If you're living at altitude in a hypoxic environment, presumably you are functioning at less than 100% mental capacity. How can you be sure that the science you do is actually any good?

JC Well we plan everything in detail before we go and we're all pretty experienced scientists and highly motivated, so this helps. The organisers of the trip take diamox (a carbonic anhydrase inhibitor) and this helps quite a bit too. We have on occasions had to send people down, though, because they got so ill. Once we were in the Alps just below the Matterhorn at about 11,000 ft. We were using a mountain hut as a lab and on the second night one guy, an experienced mountaineer, developed pulmonary

David Paterson measuring a Sherpa's blood oxygen saturation

oedema. Fortunately, we had some furosemide (a diuretic) with us. So we started him on that and then had to get him down the mountain in the dark and snow whilst collecting his copious urine output in lemonade bottles! He recovered OK, I'm pleased to say.

TL It all sounds a bit grim to me. Are there any good bits?

JC Being in such remote environments, you notice that it is absolutely pristine – stunning in fact. And this offsets the unpleasantness of the rest of the time. But it's not everyone's cup of tea by any means.

TL Any scary moments?

JC There have been a few. I suppose the most hazardous time was in a village in Peru when we came in the way of the Shining Path guerrillas and had to spend most of the night under the bed as the bank outside the lab was blown up and bullets started flying when the army was sent in!

Then there was the famous episode of the dodgy Russian we met in a bar in Kathmandu. We needed to move our gear to Lukla (9,400 ft) and he said he had a helicopter and could do it for us. David Paterson (University of Oxford) began negotiations and we ended up handing over a pile of cash and striking a deal to meet him at night in a remote field. We hired a Sherpa and a battered bus to get our stuff there but on the way our path was blocked by a huge pile of stones, which turned out to be a terrorist road block. We had to dismantle it stone by stone, not knowing whether we'd be killed at any moment.

The team waiting for signs of a helicopter

Finally, after waiting nervously in this field with our kit, the helicopter arrived very low, just about skimming the mountain tops. Flights in Nepal are monitored by the military so it could land only for a short time out of radar surveillance. We bundled our stuff in and got out OK. But it was all a bit hair-raising.

TL It all sounds very British and gung-ho.

JC Perhaps, but nevertheless good science does get done. You have to be very determined and single-minded. Although I do have to admit that for me it's an excuse to visit the high mountains as a break from my main lines of research. We have still published some important original observations on altitude sickness and sleep, though!

Publications arising from John Coote's 'holidays' at altitude include:

Coote JH, Nicholson AN, Smith PA, Stone BM & Bradwell AR (1988). Altitude insomnia studies during an expedition to the Himalayas. *Sleep* **11**, 354-361.

Smith PA, Coote JH, Nicholson AN & Stone BM (1989). Sleep during an alpine expedition. *Aviat Space Eviron Med* **59**, 478-481.

Coote JH, Stone BM & Tsang G (1992). Sleep of Andean high altitude natives. *Eur J Appl Physiol* **64**, 178-181.

Coote JH, Stang G, Baker A & Stone BM (1993). Respiratory changes and structure of sleep in young high altitude dwellers in the Andes of Peru. *Eur J Appl Physiol* **66**, 249-253.

Coote JH (1993). Sleep at high altitude. In *Sleep*, ed. Cooper R, pp 242-264. Chapman Hall, London.

Nobel Laureate to give keynote lecture at KCL in National Science Week

National Science Week (10-19 March) is an annual event run by The British Association for the Advancement of Science to provide people with an opportunity to take part in science, engineering and technology activities. This year The Physiological Society is sponsoring an event organised by Richard Siow at the Guy's Hospital Campus of King's College London on 17 March. The session will focus on recent advances in medical imaging techniques, and the keynote lecture will be given by Sir Peter Mansfield FRS (pictured right), who was awarded the 2003 Nobel Prize in Physiology/ Medicine. The lecture will include background on his pioneering achievements in magnetic resonance imaging. A major emphasis for this event will be on the diagnosis of heart diseases and Professor Peter Weissberg, the Medical Director of the British Heart Foundation, will give a short presentation on biomedical and clinical applications of medical imaging techniques, with an associated exhibition on imaging techniques currently used in the diagnosis of heart disease. This exciting event is targeted towards sixth form students and undergraduates, although anyone with an interest is welcome to attend. The event will begin at 1 p.m. with lunch and demonstrations of medical imaging equipment will be available during the afternoon. Sir Peter Mansfield will give his lecture at 4 p.m. followed by a reception for all participants.

For further programme details please contact:

Richard Siow (richard.siow@kcl.ac.uk) or **Donna Brown** (dbrown@physoc.org)

How ion channels and transporters affect metastasis

Cell migration is an important mechanism in metastasis. Ion transporters such as the Na+/H+ exchanger NHE1 control migration of tumour cells by, among other things, modulating cell adhesion. NHE1 creates a pH nanoenvironment at the cell surface that allows a coordinated formation and release of cell-matrix contacts during cell migration

Cell migration away from the primary tumour is a major step in metastasis. This multistep process requires sequential interaction between the invasive cell and the surrounding extracellular matrix as follows:

- migrating cells release matrix metalloproteinases in order to cleave their way through the dense, fibrous network of the extracellular matrix
- a directed reorganisation of the cytosekeleton, especially actin filaments, is needed for the continuous renewal of protrusive structures at the front of a motile cell
- the simultaneous action of the Na^+/H^+ exchanger NHE1, the Cl^-/HCO_3^- exchanger AE2, the aquaporin AQP1 and possibly the Na^+-HCO_3^- cotransporter NBC1 mediate local salt and water uptake at the leading edge of the lamellipodium which induces gradual cell swelling and causes the leading edge to grow (Schwab, 2001, Fig. 1)
- a coordinated formation and release of focal adhesion contacts to the extracellular matrix mediated by receptor molecules such as integrins enables the migrating cell to grab and loose its hold on the extracellular matrix.

Our interest is focused on the roles ion transporters and channels play in cell migration. One of these transporters whose role in cell migration is well studied is the Na^+/H^+ exchanger isoform NHE1. The primary task of the NHE1 is the regulation of intracellular pH and cell volume. Its housekeeping activity is of particular importance for many tumour cells. Insufficient tumour vascularization leads to a diminished O_2 supply, so that anaerobic glycolysis leads to an accumulation of protons in the cytosol. Excess protons are extruded into the extracellular space by the NHE1 which then causes an acidification of the tumour tissue.

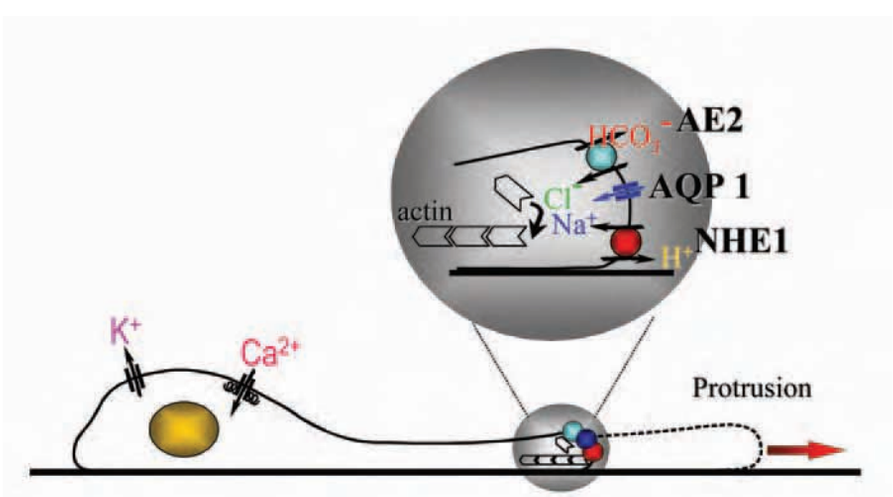


Figure 1. Model demonstrating the function of ion channels and transporters in migrating cells. At the leading edge of the cell salt uptake mediated by Na^+/H^+ (NHE1) and Cl^-/HCO_3^- (AE2) exchange and osmotic water entry facilitated by the aquaporin AQP1 occur. They contribute to the extension of the lamellipodium. Increasing volume and membrane tension eventually trigger a rise in intracellular Ca^{2+} ($[Ca^{2+}]_i$) concentration by activation of mechanosensitive cation channels. This rise in $[Ca^{2+}]_i$ induces the retraction of the rear part of a migrating cell accompanied by massive K^+ efflux and shrinkage of the posterior cell pole (modified after Schwab 2001).

Christian Stock (top) and Albrecht Schwab

NHE1 activation enhances the invasiveness of tumour cells (Reshkin *et al.* 2000; Cardone *et al*. 2005) while blocking NHE1 inhibits cell migration in several cell types. The fact that NHE1 and integrin dimers colocalize at the focal adhesion contacts led us to hypothesize that NHE1 creates a pH nanoenvironment at the surface of the plasma membrane which then affects cell migration.

To prove this hypothesis we studied the migration of human melanoma cells that utilize a2b1 integrins for establishing reversible cell-matrix contacts (Maaser *et al*. 1999). Migration of these cells depends on both NHE1 activity and the extracellular proton concentration (Stock *et al.* 2005). Cells reach their maximum motility at extracellular pH values of about 7.0 to 7.2. They hardly migrate at pH 6.6 or 7.5, when NHE1 is inhibited, or when NHE1 activitiy is stimulated by loading cells with protons. Under these different conditions characteristic changes in intracellular pH are observed. The changes in the intracellular pH,

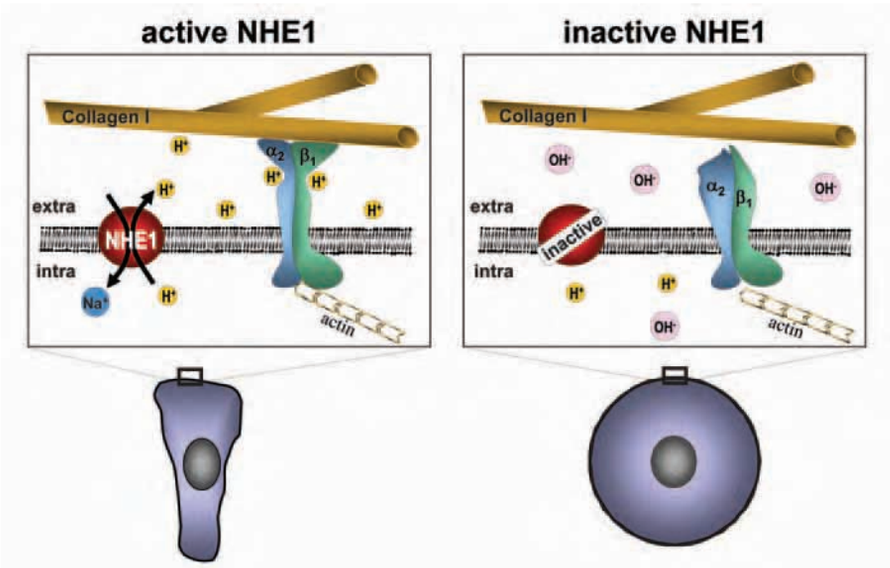


Figure 2. Model of the functional interrelation of NHE1 activity and integrin-mediated cell adhesion in human melanoma cells (MV3). NHE1 and integrins (e.g. $\alpha_2\beta_1$) are colocalized at the leading edge of the lamellipodium. Protons stabilize the collagen-integrin bond. A, normal NHE1 activity leads to suitable cell adhesion and to the formation of a lamellipodium with a leading edge. B, a lack of protons (alkalosis) or an inhibited NHE1 activity prevent adhesion and cells become spherical (modified after Stock *et al.* 2005).

however, cannot account for the changes in migratory behaviour. Migration instead correlates with the strength of cell-matrix interactions, as adhesion is strongest at an extracellular pH of 6.6 and weakens at basic extracellular pH values, upon NHE inhibition or upon blockage of the integrin $\alpha 2\beta 1$.

At this point a direct interrelation between NHE1 activity, extracellular proton concentration, cell migration and adhesion begins to appear (Fig. 2). The extracellular protons and NHE1 activity affect migration of human melanoma cells by modulating cell-matrix interactions. Migration is hindered when the interaction is too strong (acidic extracellular pH) or too weak (alkaline extracellular pH or NHE1 inhibition).

Implications

Ion transporters such as NHE1 might be potential targets for chemotherapeutics within the scope of the treatment of cancer.

For instance NHE1 inhibitors such as cariporide (also known as HOE642), have been shown to have low levels of toxicity, so that they might be useful as anti-cancer agents. Cariporide has been shown to have antiproliferative activity in vitro, and long-term treatment of rats with this drug prevents them from dying of cancer. Only time and more research will tell if NHE1 will really provide a new angle of attack on cancer, but the signs are promising.

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Multimerisation – an only transporter is a lonely transporter

David Meredith (left) and Richard Boyd.

The Oxford English Dictionary definition of a multimer is '*An aggregate of molecules held together by relatively weak bonds, such as hydrogen bonds'*.

As all biological systems include water, by this definition all proteins would be multimers – hence the need for a more physiologically relevant definition. This would not be confined to a molecular aggregate held together by weak bonds, but would include 'salt bridges' and covalent bonds; but critically in this new definition the aggregation must be between protein molecules.

A monomer transport protein is a single polypeptide chain that possesses the intrinsic capability of transporting its substrate(s) and additionally exists in the membrane without interacting with other proteins (Fig. 1*A*).

It is surprisingly difficult to find examples of membrane transport proteins cited in the literature as being shown to be monomers. One example is the bacterial lactose transporter, lac permease (reviewed in Kaback, 2005); another is the mammalian sodium/glucose cotransporter SGLT1, shown by Eskandari *et al*. (1998), with freeze fracture electron microscopy allowing measurement of the particle size of the cloned transporter expressed in Xenopus oocytes. However, even these two examples are not unchallenged: the lac permease has been suggested to be a dimer by a number of researchers, with the experimental conditions (such as the presence or absence of a physiological

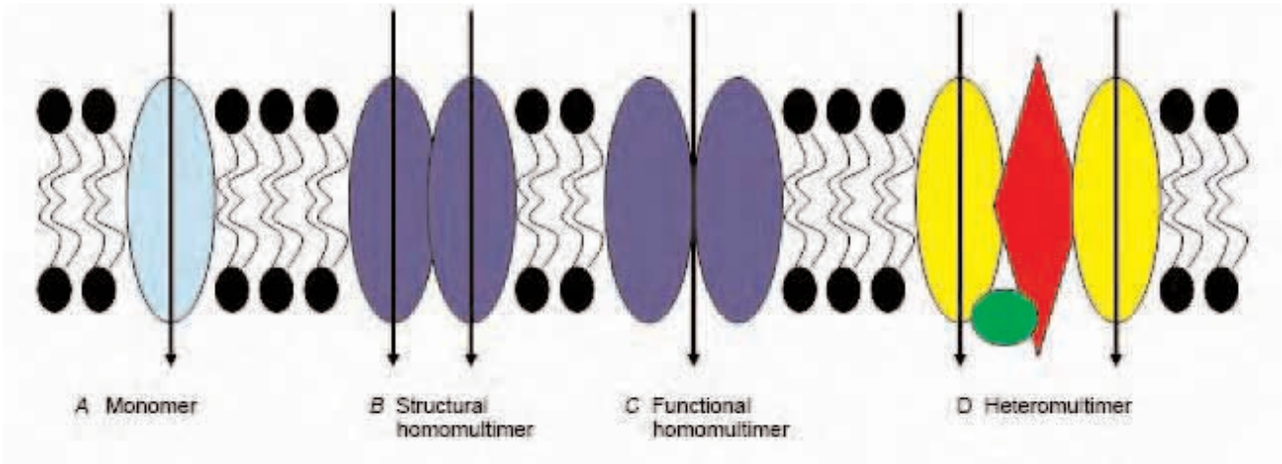

Figure 1. Cartoon to show different types of multimerisation of membrane proteins (see text for details).

electrochemical gradient (Golkorn *et al*. 1984), or the detergent used (Houssin *et al*. 1984) being proposed to affect the subunit interactions. Earlier reports from radiation inactivation experiments are consistent with proposals that SGLT1 exists as a multimer (Lin *et al*. 1984), while a decade later Koepsell & Spangenberg (1994) reported that 'the functional Na+-glucose cotransport systems in mammals are composed of two SGLT1-type subunits' (as well as a regulatory protein) using similar techniques.

A heteromultimer is a multimer (as defined above) where the subunits are not all identical. Thus it could either consist of a number of (all) different subunits/ polypeptides, or of a number of identical subunits plus one or more other distinct protein.

The topic of heteromultimeric transport proteins is too large to be given more than the briefest treatment here, but includes:

• proteins which modify the function of others e.g. the NHERF family (reviewed by Shenolikar *et al*. 2004);

• true multi-subunit transport proteins (e.g. amino acid transporters, reviewed by Verrey *et al*. 2004); or

• proteins required (at least) for expression (e.g. MCT1 and CD147, reviewed by Halestrap & Meredith, 2004).

There are two ways of defining multimers that contain two or more identical transporter polypeptides, based on the way the identical subunits interact, irrespective of whether they are in a heteromultimer or a homomultimer (where all the subunits are identical polypeptide sequences).

In a structural multimer each transporter protein subunit has the intrinsic capability of transporting its substrate, but in the membrane the protein is found associated with (at least) other polypeptides of sequence identical to that of the subunit (Fig. 2*B*).

For example, each individual subunit of SGLT1 is thought to have its own substrate binding site and translocation pathway, based on the finding that SGLT1 transports glucose when expressed in *Xenopus* oocytes yet appears as monomers in freeze-fracture electron microscopy. Thus it would appear that if/when the proteins are present as a dimer, this is because they are physically more stable in this form.

While at the present time mammalian transport proteins are virtually impossible to crystallise, more progress has been made with those from bacteria. For example, the bacterial multidrug resistance transporter EmrE has been shown to be an asymmetric homodimer (Ubarretxena-Belandia & Tate 2004), with each subunit crystallised with a tetraphenyl-phosphonium ion (TPP^+) substrate bound to it. As the binding sites were virtually central to the protein, it would be logical to speculate that each subunit might act as a transporter if in the (albeit unphysiological) monomeric state.

In a functional multimer each transporter protein subunit does not have the intrinsic capability of transporting its substrate, but has to be associated with (at least) other polypeptides of sequence identical to that of the subunit in order to function (Fig 2*C*, *D*).

The ability of a mutant subunit of a transporter multimer to inhibit the activity of a wildtype one indicates that the interaction between the subunits in the multimer is essential for the functioning of the individual subunits, that is, the individual subunits do not have intrinsic transport capability. Thus the mutant protein exerts a dominant negative effect on the wildtype proteins, and this can be measured by a drop in activity when the mutant and wildtype proteins are co-expressed in a heterologous expression system such as *Xenopus* oocytes. There are a number of explanations for why a dominant negative phenomenon might be observed, e.g. the binding site is made up of parts of a number of subunits, or a single subunit protein does not have the correct shape to be functional.

Analysis of the reduction of transport when known ratios of mutant and wildtype protein are expressed, with an assumption of a binomial distribution of mutant and wildtype protein complexes, allows modelling of the data to estimate the number of subunits

in the multimer. This approach was used by Casula *et al*. (2001) for the KCC1 K-Cl cotransporter, and in our laboratory for the proton-coupled peptide transporter PepT1 (Panitsas *et al*. 2006). Data from such an experiment on PepT1 is shown in Fig. 2*A*. The model that best fits the data (shown by the solid line) represents a tetramer, with at least two wildtype subunits (Fig. 2*B*). One conclusion would be that the mutant PepT1 shows a dominant negative effect, and that the tetramer actually consists of a dimer of functional dimers (Fig. 2*C*).

Why is it important to know whether a transport protein is a monomer or a multimer, and, if the latter, of what type? There is a paucity of high resolution structures for membrane transporters, and computer modelling is one way of providing a working model. Therefore, if the protein of interest is for example a functional multimer, this will be crucial information. In a very recent paper by Jen *et al*. (2005), a heterozygous mutation was identified in a neurotransmitter reuptake system for glutamate (EAAT1) in a patient with episodic ataxia, seizures, migraine and alternating hemiplegia. When the mutant EAAT1 was expressed with the wildtype (as would happen in a heterozygous individual) the function of the wildtype was severely compromised. The decreased glutamate uptake is predicted to result in the neuronal hyperexcitability and the symptoms reported.

Therefore, multimerisation is not just of academic but also of clinical importance.

Acknowledgement

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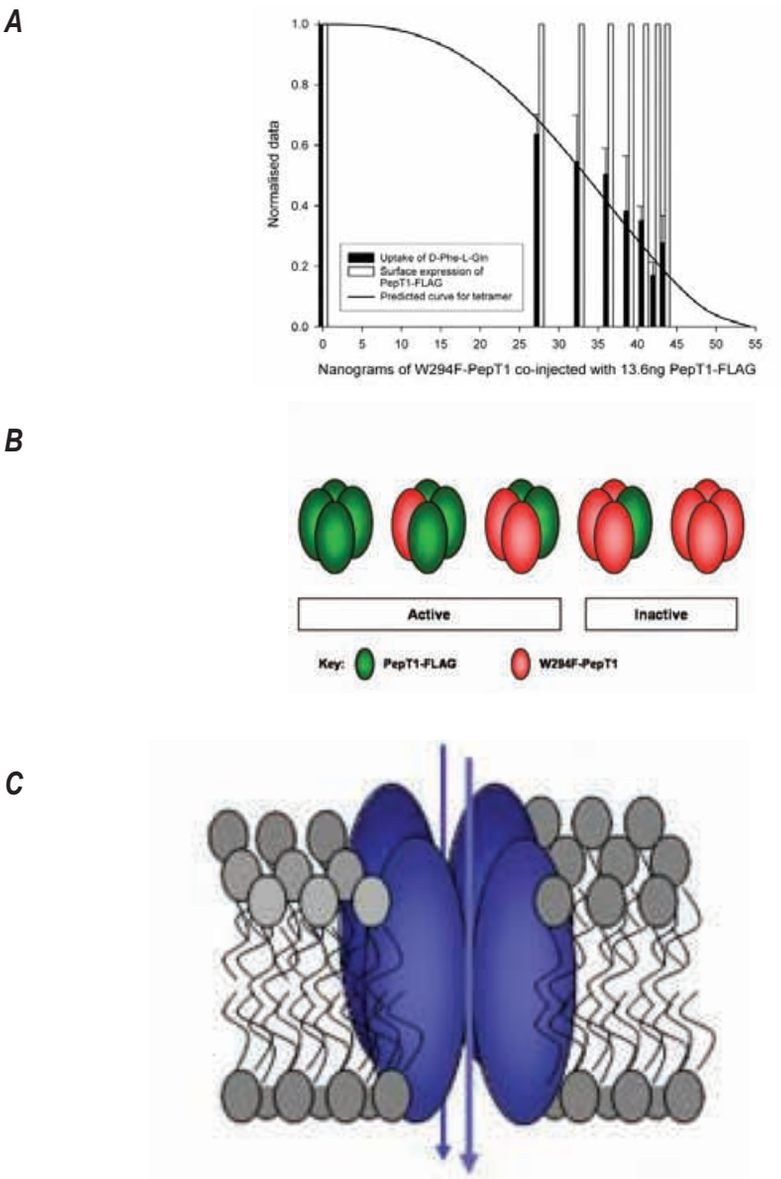

Figure 2. *A,* Data modified from Panitsas *et al*. (2006) showing the uptake of dipeptide into oocytes (filled bars) and the membrane surface expression of PepT10FLAG)open bars) with injection of increasing amounts of cRNA for the non-functional mutant PepT1 transporter (W294F-PepT1) and a constant amount of cRNA for the functional PepT1 (PepT1-FLAG). The line represents the model that best fits the data, which is that of a tetramer with at least two functional subunits. *B,* Cartoon to explain data in Figure 2*A*. *C,* Cartoon of a possible model of PepT1 in the membrane, forming a dimer of functional dimers.

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A new muscle sense?

Uwe Proske proposes that, whenever movement of our limbs is accompanied by an effort sensation, this information can be used by the brain to determine the location in space of the limbs

In a previous report (*Physiology News* **60**, 14), I described our work on muscle exercise and how intense exercise of arm muscles, be it eccentric or concentric, can lead blindfolded subjects to make positional errors in a forearm matching task. The observations prompted us to propose that the muscle activity required to hold up the arm against the force of gravity provides us with information about where the arm is in space (Walsh *et al.* 2004). That is our new sense!

At the present time the generally accepted view is that muscle receptors, specifically the muscle spindles, provide us with our sense of limb position and movement. This view is firmly based on experimental observations. In 1972, Goodwin, McCloskey and Matthews showed that muscle vibration produced illusions of both movement and changed position of the forearm during vibration of elbow flexors (Goodwin *et al.* 1972). Since the primary endings of spindles were known to be selectively sensitive to vibration, the observations led to the present-day view that the kinaesthetic sense (position and movement) is generated by signals of a peripheral origin. Our observations, if confirmed, will require these ideas to be modified.

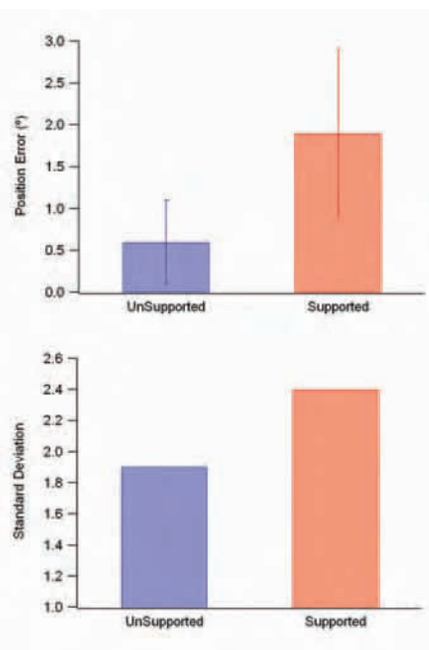

Figure 1. Forearm position errors. Blindfolded subjects had their forearms taped to paddles which were hinged at a point coincident with the elbow joint. Elbow angle was recorded with potentiometers. The experimenter placed one forearm at a given angle and the subject matched its position with their other arm. Errors for 11 subjects were calculated from the differences in angles between the two arms. Upper panel: Mean position errors (±SEM). Blue histogram, subjects held the reference arm unsupported at the test angle. Red histogram, the relaxed reference arm was placed on a support during position matching. Lower panel: Mean standard deviations of position errors. Blue, unsupported, red supported (Redrawn from Winter *et al*. 2005).

When we say that subjects derive spatial information from their sense of effort we mean that a certain amount of effort is required to hold the arm in a given posture against the force of gravity. If the arm is more horizontal, the gravitational vector will be larger, requiring more muscle activity to hold it there. The extra activity is perceived as more effort (Walsh *et al*. 2004). The actual relationship between effort and position is complicated by the fact that muscle force and torque at the elbow joint don't change in parallel with change in angle, since the moment arm changes and muscle length changes too. In any case, we propose that for a given effort required to support the arm against gravity, the brain is able to derive information about its position in space. How the sense of effort is calibrated is another matter.

The idea that our muscle senses may have a central origin is not new. Von Helmholtz proposed a 'sensation of innervation' back in 1867. Since then the question of whether a proprioceptive signal is associated with the motor command has been repeatedly raised. For example, the present-day view of the sense of force or of heaviness is that it is derived centrally. The evidence is that force and heaviness matching can be disturbed by weakening the muscles with partial paralysis or fatigue. For a review, see (McCloskey *et al.* 1983).

As far as we know, it has not been specifically claimed before that the motor command can also provide positional information. In 1988 Peter Matthews declared, '… the interest now is not in asking simply whether corollary discharges are involved in the genesis of human position sense, for it seems to me that they must be' (Matthews, 1988). By corollary discharges Matthews meant a copy of the central motor command. Be that as it may, there have been few specific proposals put forward which incorporate a central command signal in the perception of limb position. Thus Worringham and Stelmach (1985) concluded that torque sensation was an accessory source of information in limb positioning. Other reports have tended to interpret their observations in terms of an exclusively peripheral origin of the positional signals (Rymer & D'Almeida, 1980).

We propose that positional information from the sense of effort is available only when positioning of the limb is accompanied by muscle contraction. Does that mean the sense of effort plays a role in kinaesthesia only when the limb is held against the force of gravity? We think not. We are coming to the view that for all limb placements that involve muscle contraction, even in circumstances which are gravity-neutral, such as moving the arm in the horizontal plane, effort plays a role in position sense.

What happens when there is no muscle activity and the muscle remains relaxed? If a blindfolded subject places their arm at a set angle on a support and the arm remains relaxed, position sense is rather poor, with subjects routinely making large matching errors (Winter *et al.* 2005). However, as soon as they support their arm themselves, their matching performance improves significantly (Fig. 1).

In another experiment we have been able to provide evidence that the crude

position signal available to subjects when their arm is relaxed is coming from muscle spindles (Winter *et al.* 2005). The evidence is based on the observation that conditioning the muscle at different lengths leads subjects to make systematic errors in position sense (Fig. 2). The reason for this pattern of errors is that the contraction has conditioned the responses of the muscle spindles.

When a muscle is contracted voluntarily, both skeletomotor and fusimotor neurones are co-activated (Vallbo, 1974). This means that the intrafusal muscle fibres of spindles contract. If that is done in a posture where the muscle is short, and afterwards the muscle is stretched to an intermediate length, the intrafusal fibres will be taut and spindle resting discharge levels will be high. Alternatively, the muscle is contracted while holding the limb in a posture where the muscle is long. On moving it to a shorter length, the intrafusal fibres will fall slack and therefore resting discharge will be low (Gregory *et al.* 1988). Such contraction history-dependent changes in spindle activity are reflected in the observed errors in position sense (Fig. 2). This is a powerful argument for spindles as the receptors responsible since other sensory receptors that might contribute, skin and joint receptors, are unlikely to show such history-dependent behaviour. Effort cannot play a role since the muscle has remained relaxed.

So, to summarise up to this point, when our limb muscles are relaxed, positional information is coming from muscle spindles. However, as soon as the task requires some muscle contraction, additional information from another source begins to contribute. We claim that this source is the sense of effort, generated centrally in association with the motor command.

Our current area of research concerns the changes in position sense observed when the limb is bearing a load. As already mentioned, during a voluntary contraction spindles become co-activated. The fusimotor activity might be expected to produce a sudden change in the position signal. Yet the observations are of a smooth transition from passive position matching to where the muscles are contracting (Fig. 2). We place particular importance on the observation that the conditioning effects gradually disappear as load increases. Fusimotor-activated spindles would not be expected to show muscle conditioning effects, since any slack introduced by conditioning would be taken up by the fusimotor activity (Gregory *et al*. 1988). During a contraction, while the effects of muscle conditioning are significantly less, for a submaximal contraction (15% of maximum in Fig. 2), some small conditioning effects persist. This suggests that the few remaining passive spindles are still able to manifest themselves as position errors.

What we are saying is that evidence of a spindle contribution to position sense in the passive muscle, and for low levels of contraction, is clearly discernible. Then, as the contraction grows, a new influence becomes apparent. Our experiments suggest it is the sense of effort. In an alternative view, spindles continue to provide the position signal but after some kind of central processing of their input, where fusimotor-related activity is subtracted out (McCloskey *et al.* 1983). To resolve this issue is a challenge for the future.

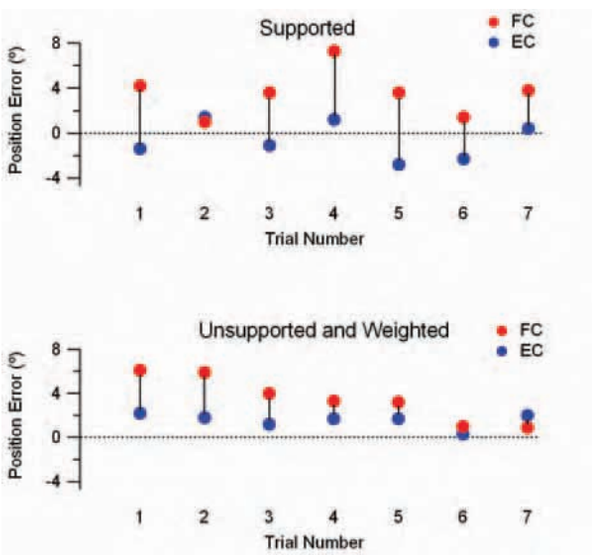

Figure 2. Effects of muscle conditioning on position sense.
Upper panel: Distribution of position errors for a single subject after a conditioning voluntary contraction of the reference arm with the arm held extended (blue dots, EC) or held flexed (red dots, FC). After conditioning, the relaxed reference arm was placed on a support at the target angle. Trials alternated between the two forms of conditioning and each pair of measurements has been joined by a line. Errors are scored as positive in the direction of extension and negative in the direction of flexion. The dotted line is zero error, i.e. where reference and matching arms were exactly aligned. Lower panel: similar measurements made while the reference arm was held by the subject themselves at the test angle, unsupported. The paddle to which the arm was strapped had 2kg of weight attached with it, meaning that an elbow flexion force of approximately 15% of maximum was required to maintain arm position (Redrawn from Winter *et al*. 2005).

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Sympathetic nerve activity and cardiac output: an integrated balance with implications for blood pressure regulation

Sympathetic vasoconstrictor nerves have an important role in blood pressure regulation in humans via control of peripheral vascular resistance. Recent findings of a balance between cardiac hemodynamics and control of sympathetic activity at rest provide insight into integrated mechanisms of blood pressure regulation in individuals with widely varying sympathetic activity

Gunnar Wallin (left), Michael Joyner and Nisha Charkoudian

Sympathetic vasoconstrictor neural activity (SNA) is a major contributor to blood pressure regulation in humans: a rise in SNA increases vasoconstriction and vascular resistance, resulting in an increase in blood pressure. It has long been considered paradoxical, therefore, that humans with higher resting SNA do not necessarily have higher blood pressures than those in whom SNA is very low. Indeed, there is wide inter-individual variability in SNA among normotensive humans with similar arterial pressures. Furthermore, muscle SNA (MSNA, often measured in humans) is extremely reproducible over time (Fagius & Wallin, 1993), and correlates well with resting SNA in other vascular beds (Wallin *et al.* 1996). Yet MSNA can vary 5-10 fold among individuals (Fagius & Wallin, 1993; Charkoudian *et al.* 2005). Thus if we consider that mean arterial pressure is determined by the product of cardiac output and total peripheral resistance (MAP = CO x TPR), we must ask the question: how can all this variability exist in normal healthy individuals with similar blood pressures?

We recently set out to investigate this apparent paradox by testing the hypothesis that a balance exists between CO and MSNA that is important to normal blood pressure regulation. We further hypothesized that this balance would involve an inhibitory influence of CO on baroreflex control of MSNA. To address these hypotheses, we measured MSNA (peroneal microneurography), CO (acetylene uptake) and arterial pressure (directly via radial artery catheter) in 18 normotensive men (Charkoudian *et al.* 2005). Our most striking finding was a strong inverse relationship between CO and MSNA, such that individuals with high CO tended to have low mean levels of MSNA, and vice versa. Figure 1*A* shows the relationship between CO and MSNA at rest among our subjects. Furthermore, MSNA showed a positive correlation with TPR in our subjects, as shown in Figure 1*B*. Taken together, these relationships suggested a balance between the two main contributors to arterial pressure: CO and TPR (Charkoudian *et al.* 2005). The findings provide strong evidence that a major reason why individuals with higher sympathetic nerve activity do not have higher blood pressures is because of a balance between cardiac hemodynamics and control of peripheral vascular resistance.

Previous microneurographic recordings of human MSNA have revealed that, in individual subjects, the arterial baroreflex exerts substantial control over MSNA. Thus small changes in blood pressure elicit marked opposing changes in MSNA, which tend to correct, or 'buffer', the original changes in pressure (Kienbaum *et al.* 2001; Charkoudian *et al.* 2004). Given this strong baroreflex control, it is quite

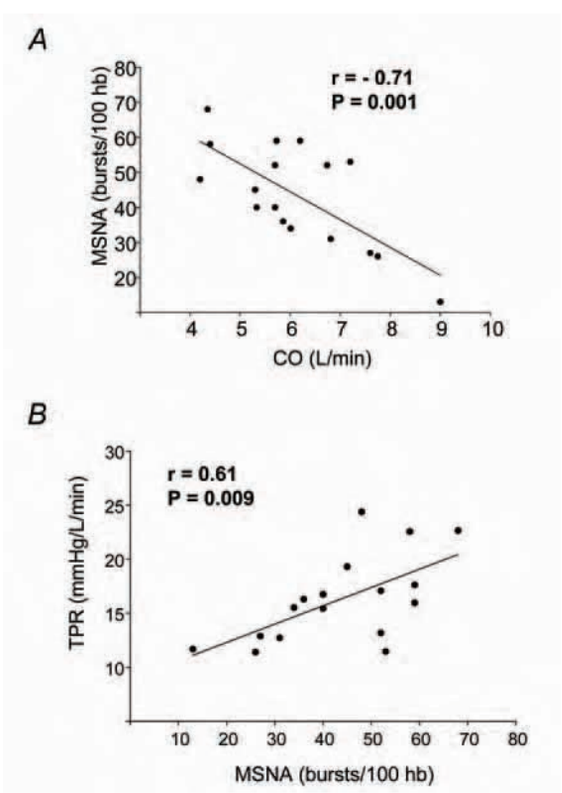

Figure 1. ***A*** Inverse relationship between cardiac output (CO) and MSNA at rest among normotensive subjects, such that individuals with high resting MSNA have low CO, and vice-versa. ***B*** Direct relationship between MSNA at rest and total peripheral resistance (TPR), showing that MSNA is probably a good indicator of total 'net' sympathetic vasoconstrictor tone at rest.

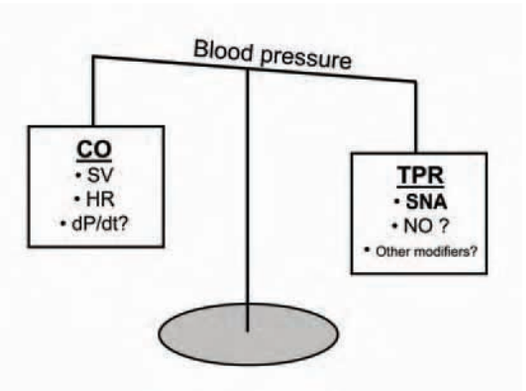

Figure 2. Schematic diagram showing the balance between cardiac output (CO) and total peripheral resistance (TPR) in regulation of blood pressure. Represented in the figure is the major role our data suggest for a balance between sympathetic nerve activity (SNA) and CO in this overall regulation. Other potential influences on the integrated regulation may include stroke volume (SV), rate of change of pressure (dP/dt), and factors that may influence vascular responsiveness to SNA, such as nitric oxide (NO).

striking that the large inter-individual variability in MSNA in normotensive humans results in a complete lack of correlation between mean levels of nerve activity and blood pressure across individuals (Skarphedinsson *et al.* 1997; Charkoudian *et al.* 2005). In our recent study, we reasoned that this lack of correlation might be explained by an influence of CO on baroreflex control of MSNA (Charkoudian *et al.* 2005). We assessed this possibility using a technique called 'threshold analysis', which gives information about how likely it is that a given level of blood pressure will elicit a burst of sympathetic activity. The midpoint (T50) of a threshold diagram provides a measure of the blood pressure value which elicits a burst of sympathetic activity 50% of the time (for detailed discussion, see Kienbaum *et al.* 2001). We found that CO and stroke volume (SV) were each inversely related to T50 among our subjects, suggesting that high resting CO and SV may inhibit sympathetic outflow at rest via the baroreflex.

The inverse relationship we observed between CO and MSNA, and the apparent inhibitory influences of CO and SV on baroreflex control of MSNA, suggest that a balance between CO and SNA is an important element of normal blood pressure regulation. This is shown schematically in Fig. 2, along with factors that may influence this balance. From the cardiac perspective, the influence of SV may be important, via afferents from the cardiopulmonary region (Charkoudian *et al.* 2004), and/or by its effects on the rate of change of pressure (dP/dt) which could alter afferent firing of arterial baroreceptors (Chapleau & Abboud, 1989). The relationship between SNA and total peripheral resistance (TPR) in this balance may be affected by one or more of numerous influences on vascular tone. For example, Skarphedinsson *et al*. (1997) reported a direct relationship between circulating nitrite/nitrate (a plasma marker of nitric oxide activity) and resting MSNA among normotensive males. This suggests that individuals with higher SNA also have higher circulating nitric oxide, and that its vasodilator effects may offset vasoconstrictor influences of high sympathetic activity.

Our recent results do not address the origin of the inter-individual variability in MSNA or CO. Some evidence suggests that the variability in the MSNA/CO relationship may be genetic in origin. For example, identical twins have very similar levels of resting MSNA (Wallin *et al.* 1993) and genetic variation in genes encoding the beta-adrenergic receptor cause differences in CO and hemodynamic responses (Eisenach *et al.* 2005). It will be interesting to see whether it is possible in the future to identify genetic factors which contribute specifically to the balance of factors described here.

The existence of a balance between CO and MSNA leads to the intriguing possibility that the bases for some forms of hypertension may be that individuals are 'out of balance' in this regard – their level of CO is too high for the level of MSNA, or vice-versa. Taking both elements of the CO-MSNA balance into account may help to explain previously contradictory reports regarding whether individuals with hypertension have higher SNA compared to healthy controls (Gudbjornsdottir *et al.* 1996). In a broader sense, better understanding of the integrated balance of the mechanisms presented here (and other potential contributors) will not only improve our understanding of the complex physiology involved, but may, in the future, lead to more individualized diagnostic assessment and treatment of certain forms of cardiovascular malfunction.

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Ca^{2+} sparks – SOS signals of struggling muscle

Ca^{2+} sparks are rare in mammalian skeletal muscle under physiological conditions. Our recent studies reveal an important role for mitochondria in suppression of these localized Ca^{2+} signals

The primary function of skeletal muscle is to produce shortening and force for movement of our bodies. A complex series of events, known as excitation-contraction coupling (ECC), links nerve-mediated electrical excitation of the skeletal muscle membrane to muscle contraction. A key step in ECC is the release of Ca^{2+} from intracellular Ca^{2+} stores (sarcoplasmic reticulum, SR) to activate the contractile machinery. Ca^{2+} release occurs through specialized Ca^{2+} channels, called ryanodine receptors (Ryrs). For several decades it was believed that Ca^{2+} release channels are opened by mechanical interactions with the voltage-sensing molecules of the T-tubular membrane (dihydropyridine receptors) and that Ca^{2+} released from the SR by this voltage-dependent mechanism subsequently activates additional Ryrs via Ca^{2+}-induced Ca^{2+} release (CICR), thereby amplifying the contractile signal.

The phenomenon of CICR was discovered in mechanically skinned fibres in the early1970s (Endo *et al*. 1970) but for a long time there was no direct evidence of its involvement in Ca^{2+} signaling during ECC.

From left: Elena Isaeva, Vyacheslav Shkryl and Natalia Shirokova

Direct experimental evidence for CICR function in normal skeletal muscle physiology was provided only in 1995, when Ca^{2+} sparks were found in amphibian skeletal muscle. Sparks, transient localized elevations of cytosolic [Ca^{2+}], represent SR Ca^{2+} release events through a small cluster of Ryrs, and are considered to be elementary events of CICR. They are abundant in frog muscle fibres and their frequency is greatly increased by electrical stimulation, suggesting a substantial contribution of CICR to ECC. Was the missing link of ECC definitively found? No! In mammalian muscle, spontaneous Ca^{2+} sparks are rarely seen and depolarization does not induce Ca^{2+} sparks, but Ca^{2+} 'embers', which probably result from the opening of a single Ryr channel and do not involve CICR. The latter observations left us with burning questions: why are there no Ca^{2+} sparks in mammalian muscle? Is there a fundamental difference in Ca^{2+} signalling between mammals and amphibians?

In the search for answers, several hypotheses have been considered, but most turned out to be dead-end roads. Initially, it had been suggested that the expression of the Ryr3 isoform might be necessary for skeletal muscle to produce Ca^{2+} sparks, because most amphibian, but not adult mammalian, muscles express Ryr3. However, this hypothesis did not survive experimental challenge as spontaneous Ca^{2+} sparks were found in developing skeletal muscle of Ryr3-knockout mice. Alternatively, in Shirokova *et al*. (1999), we proposed that a functional interaction between DHPrs and Ryrs prevents CICR. But this idea was subsequently challenged by Kirsch *et al.* (2001), who demonstrated abundant sparks in mechanically skinned mammalian fibres, where the coupling between DHPrs and Ryrs is presumably preserved. This indicated that mammalian fibres are capable of producing Ca^{2+} sparks, but these are normally suppressed, and immediately raised another question: why would skinning of the cells lead to the appearance of Ca^{2+} sparks?

Our recent studies revealed an important role of mitochondria in the suppression of sparks in mammals. For a long time, the almost exclusive function of mitochondria in skeletal muscle was considered to be production of the energy (ATP) supply necessary for the key muscle function – contraction. However, increasing evidence indicates that mitochondria exert a multifactorial influence on cell physiology: the organelles can

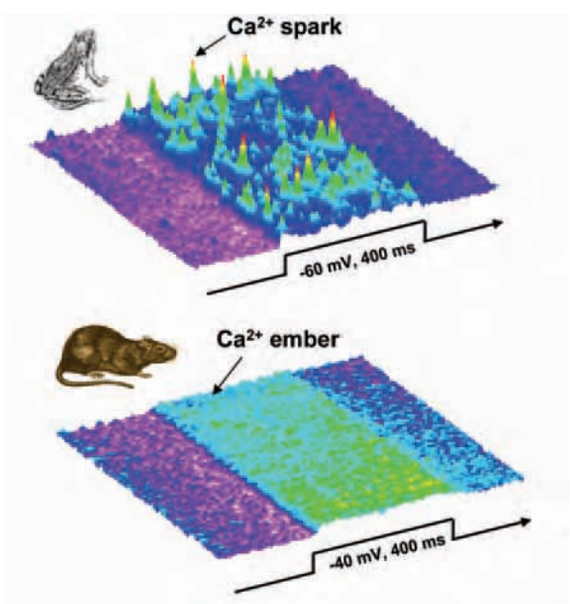

Figure 1. Membrane depolarization produces Ca^{2+} sparks in amphibian, but not mammalian, skeletal muscle.

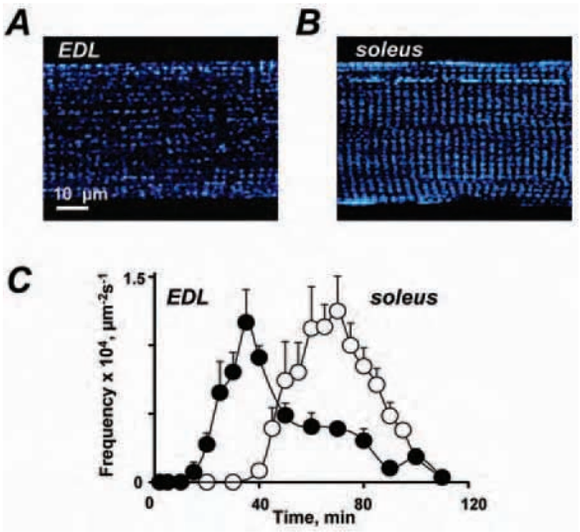

Figure 2. Ca^{2+} sparks appear earlier in skinned mammalian muscle fibres containing fewer mitochondria.
A, B Images of NADH fluorescence obtained with two-photon confocal microscopy from *EDL* and *soleus* muscle fibres, respectively.
C Development of sparks in 17 *EDL* (black circles) and 17 *soleus* (white circles) fibres. Frequency of sparks was determined from sets of 40 sequential fluo-3 images acquired with a confocal microscopy at different times after fibre permeabilization.

accumulate Ca^{2+}, produce reactive oxygen species (ROS), balance cytosolic redox potential, etc. Each of these functions is influenced by, and can in turn influence, intracellular Ca^{2+} homeostasis. Importantly for the interactions within these Ca^{2+} dependent feed-back loops, in mammalian muscle, mitochondria are strategically located close to the SR Ca^{2+} release sites, where they are capable of interfering with and sensing SR Ca^{2+} release (Shkryl & Shirokova, 2005).

How can mitochondria suppress CICR? In Isaeva & Shirokova (2003) we first suggested that a degradation of mitochondrial function following muscle permeabilization and consequent washout of cytosolic constituents is a proximate cause for the appearance of Ca^{2+} sparks in permeabilized mammalian fibers. Experiments with several mitochondrial uncouplers and Ru360, a specific inhibitor of mitochondrial Ca^{2+} uptake, revealed a potential role of mitochondrial Ca^{2+} buffering in the inhibition of CICR, as impairment of mitochondrial Ca^{2+} uptake boosted spark activity. In search of other mechanisms for mitochondria to affect cytosolic Ca^{2+} signals we next studied the appearance of sparks in permeabilized skeletal muscle fibres with different mitochondrial content (Isaeva *et al.* 2005). The results were striking: in all fibre types, Ca^{2+} sparks developed in parallel with the decay of the mitochondrial redox potential. Moreover, the appearance of sparks was delayed or sped up by the addition of exogenous ROS scavengers or ROS generators, respectively. These findings strongly implied that Ca^{2+} sparks occur when ROS increase in the cytosol as the redox potential falls upon impairment of mitochondrial metabolism. In agreement with this view, sparks were reported in intact mammalian muscle cells in response to osmotic stress or strenuous exercise (Wang *et al*. 2005), conditions in which the cytosolic ROS balance is likely to be compromised. Interestingly, it also turned out that stress-induced Ca^{2+} spark activity was significantly augmented in muscle fibers dissected from *mdx* mice lacking dystrophin, a widely used model of muscle dystrophy. This last observation suggests that Ca^{2+} sparks, although not the mediator of Ca^{2+} signaling in normal ECC of mammals, may play an important role in muscle pathology.

In summary, it is clear that CICR is less important for mammalian skeletal muscle ECC under physiological conditions than for amphibian muscle. Mammalian fibres have two triadic junctions per sarcomere whereas lower animals have only one. Ca^{2+} released from the SR in mammals thus needs to travel a shorter distance to activate the contractile machinery of the muscle. Therefore, a further amplification of the initial voltage-induced Ca^{2+} signals by CICR may not be necessary. Under stress, however, a moderate augmentation of cytosolic Ca^{2+} signals may be required for muscle adaptation. In particular, increased cytosolic Ca^{2+} concentration could lead to a mild increase of the mitochondrial Ca^{2+} load. This, in turn, can counteract the decreased mitochondrial metabolism by stimulating ATP synthesis, thereby improving muscle contractility. Under pathophysiological conditions associated with mitochondrial dysfunctions, acute and exaggerated Ca^{2+} spark activity could be a precursor of muscle degeneration.

It still remains to be clarified exactly which mitochondrial mechanisms normally suppress CICR in mammals, to what extent this suppression can be impaired in muscle diseases, and how a failure of this suppression is involved in muscle pathophysiology. It may turn out that some of these mechanisms could be targets for pharmacological interventions to slow down, or prevent, the progression of degenerative muscular conditions.

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Dying for a good night's sleep

Obstructive sleep apnoea, characterised by excessively loud snoring is not only embarrassing for the patient who falls asleep in public but has much more serious consequences – an increased risk of cardiovascular morbidity and mortality

Obstructive sleep apnoea (OSA) is a common, and yet often under-diagnosed and under-recognised, clinical disorder. It is more common in men aged 30-65 years, but can occur in all age groups, and is estimated to affect approximately 4% of middle-aged men and 2% of middle-aged women in the UK. OSA is defined as a cessation in airflow for at least 10 seconds during sleep despite continuing respiratory effort. It occurs as the result of obstruction to the upper airways, most commonly caused by excess fat due to obesity. During sleep, upper airway muscles relax and their tone is reduced. Inspiration also helps to favour airway collapse due to negative pressure within the airway. These factors combined, together with excess parapharyngeal fat or some other obstructive factor, result in closure of the airways. As a result hypoxia and hypercapnia develop, with oxygen saturation levels falling below 50% in severe cases. Fortunately, this leads to an arousal which acts to increase muscle tone and open up the airways so breathing can resume. Sleep then ensues and the cycle starts over. This cycle can occur from five times (the clinical definition of OSA) to more than 100 times per hour of sleep. Clearly this leads to severe sleep fragmentation, which is more deleterious than sleep deprivation. The most common symptom of this condition is excessive daytime sleepiness (Fig. 1).

Victoria Cooper

Aside from the impact sleepiness has in social functioning, work performance and driving ability, there are more sinister consequences to OSA. There is increasing evidence that OSA has direct and deleterious effects on cardiac and vascular structure and function, with OSA patients at increased risk of arterial hypertension, heart failure, cardiac ischemia, arrhythmias and stroke. The prevalence of hypertension in patients with severe untreated OSA may be greater than 50%, and the incidence of OSA in hypertensive patients is greater than 25%. The incidence of OSA in resistant hypertension is even greater, with one study reporting that 87% of hypertensive patients refractory to maximal medical therapy had undiagnosed OSA (Logan *et al.* 2001).

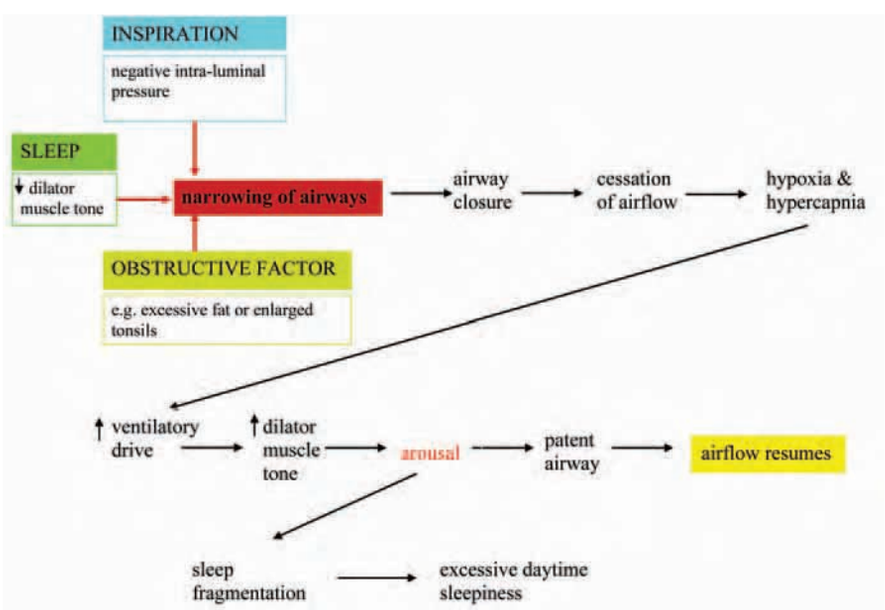

Figure 1. Pathogeneis of obstructive sleep apnoea.

The mechanisms by which OSA leads to hypertension and other cardiovascular disorders have undergone much research in recent years. Although there is no apparent consensus, the mechanisms are clearly multi-factorial. Episodes of OSA result in large swings in intrathoracic pressure, arterial oxygen desaturation, hypercapnia and acidosis. Events terminate in arousal and are accompanied by marked surges in arterial pressure, preceded by an increase in sympathetic vasoconstrictor tone. All these factors probably have some role to play in the development of cardiovascular complications.

One of the first mechanisms to be considered in the link between OSA and hypertension was that both are manifestations of a common cause, e.g. obesity. This is an attractive hypothesis since there is a known association between obesity and both hypertension and OSA. However, numerous studies have shown that even after adjustment for body mass index, although the strength of the association is predictably reduced, there is still an independent link between OSA and hypertension. Also against this hypothesis is the finding that successful treatment of OSA, particularly using nasal continuous positive airway pressure (nCPAP), reduces blood pressure despite no alteration in weight.

Frequent arousals result in abnormal electrophysiological sleep structure, in particular a reduction in the deep sleep stages 3 and 4. Arousal also results in

transient increases in heart rate, blood pressure, ventilation and surges in sympathetic output. It has been suggested that movement arousals also influence daytime sympathetic tone independently of respiratory disturbance index (the number of >3% desaturations per hour of sleep) and night-time saturation (Loredo *et al*. 1999). However, animal models have not shown arousal in itself to lead sustained hypertension (Brooks *et al*. 1997).

Probably of more importance than arousal is the effect of repetitive hypoxia and hypercapnia. Animal models have suggested that intact carotid chemoreceptors, sympathetic nervous system, renal nerves and activation of the renin-angiotensin system are all critical to the rise in blood pressure in sleep apnoea-induced hypertension. We have recently shown that brief periods of asphyxia or hypercapnia result in resetting of the carotid baroreflex to maintain arterial pressure at a higher level, and that this is sustained after the removal of the stimulus (Cooper *et al.* 2004a, 2005). This is also true for sympathetic activation (Morgan *et al.* 1995). Indeed, augmented resting (waking) sympathetic activity and a potentiated chemoreflex response to hypoxia have been found in patients with OSA (Narkiewicz *et al*. 1999). Renal handling of sodium and water is also impaired in OSA. Hypoxia leads to a deficit in renal sodium excretion and this may lead to volume expansion and hypertension. Hypoxia also has cellular effects, particularly on vascular endothelial cells. This may directly affect vascular remodelling, reactivity and resistance vessel tone, all factors which may promote hypertension.

Another point to consider is the effect of night-time surges in blood pressure on arterial baroreceptors. Baroreflexes act to maintain blood pressure at a given level, but may reset when pressure is altered for a prolonged period, so that pressure is maintained at the new prevailing pressure. A canine model of sleep apnnoea suggested that the baroreflex curve is shifted to the right without a change in slope (Brooks *et al*. 1999). We have also recently found something similar in patients with OSA. The baroreflex 'set point' (the pressure corresponding to maximal slope) is shifted to the right first thing in the morning in OSA patients, whereas the reverse is true in healthy control subjects who have a reduced blood pressure during sleep (Cooper *et al.* 2004b). We propose that night-time reductions in blood pressure during normal sleep act to reset baroreceptors towards lower levels, and that this may be a protective mechanism. This mechanism is absent in OSA and is actually reversed, which would therefore promote hypertension.

Other possible factors to be considered are changes in endothelial cell function and also insulin resistance, which is a known risk factor for atherosclerosis and thus cardiovascular and cerebrovascular disease.

In summary, OSA causes alterations in chemoreflex and baroreflex function, sympathetic tone, insulin resistance and endothelial cell function. These alterations, through a number of mechanisms, will promote hypertension and cardiovascular disease. Whatever the underlying mechanism, the increased risk of cardiovascular morbidity and mortality in patients with OSA is real. Therefore early diagnosis and treatment is essential in reducing this risk.

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Rob Clarke

Alison Marshall, Rob Clarke's sister, ran the Robin Hood half marathon to raise funds for Cancer Research UK in memory of Rob Clarke who died in August 2004 (*Physiology News* 2004, **57**, 49). Alison raised £587 for the charity.

The Journal of Physiology back issues

Two sets of *The Journal of Physiology* are on offer to any Members or their departments with space to accommodate them.

The first set offers issues of *The Journal* from **1995-2003**. Anyone interested should contact Atticus H Hainsworth at De Montfort University (AHainsworth@dmu.ac.uk).

The second set runs from **1940-2002**. Anyone interested should contact Jane Mellanby at the University of Oxford (jane.mellanby@psy.ox.ac.uk).

Benevolent Fund

The Annual General Meeting of the Benevolent Fund will be held on Wednesday, 26 April 2006 at 2 p.m. at The Society's London Administration Office.

All those who have donated to the Fund are welcome to attend.

Further details are available from Elfa Wilmot at the London Office (ewilmot@physoc.org).

Vagal nociceptors in the oesophagus

Nociceptors, in Sherrington's classic definition, are now exactly one hundred years old, but they keep turning up in new places. Here Marian Kollarik and Bradley Undem describe one example

In his timeless text on the integrated action of the nervous system, Sherrington discussed specific types of sensory nerve fibres in the skin that 'Instead of but one kind of stimulus being their adequate excitant, they may be regarded as adapted to a whole group of excitants, a group of excitants which has in relations to the organism one feature common to all its components, namely a *nocuous* character' (Sherrington, 1906). He reasoned that such nerve fibres 'under selective adaptation, attach to the skin a so-to-say specific sense of its own injuries'. The term given to this special type of afferent nerve is nociceptor. It naturally would be useful for the organism if organs other than the skin also have a 'specific sense of their own injuries', and indeed nociceptors have been identified in virtually every visceral tissue. In modern usage the term 'nociceptor' is often, explicitly or implicitly, narrowed to include only sensory nerves that mediate pain. This change in characterizing nociceptors, from the nature of their activators to the consequences of their activation, has a major influence on the type of afferent nerves that are categorized as nociceptors. It is unknown at this time whether stimulation of any type of vagal afferent nerve in the oesophagus can overtly lead to pain, yet it would seem clear that there are vagal afferent nerves that can be accurately characterized as nociceptors. Our recent studies have served to add support for this contention (Yu *et al.* 2005).

Marian Kollarik (left) and Bradley Undem

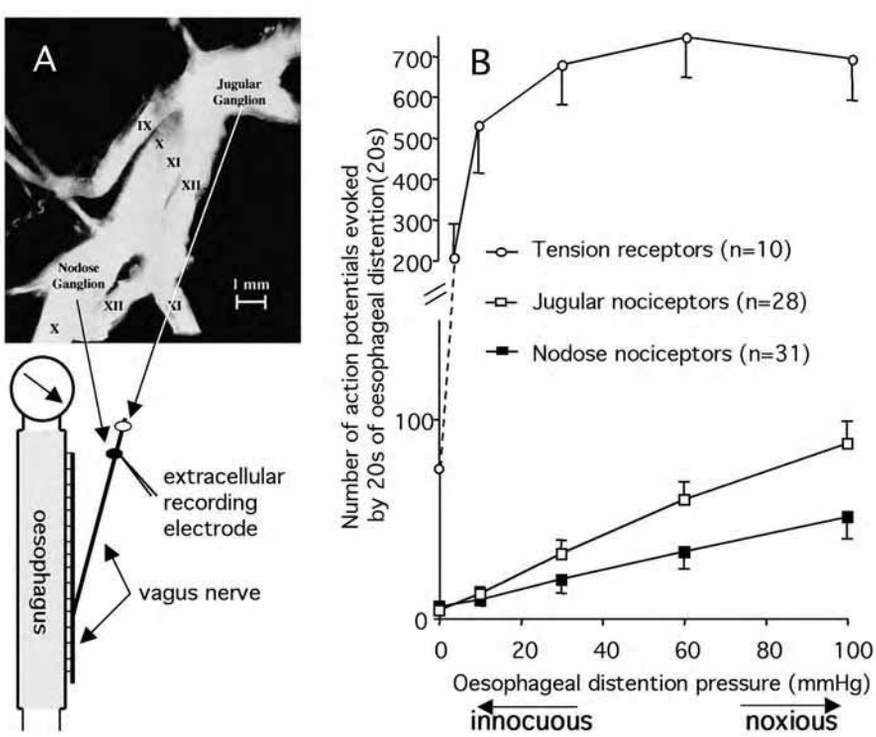

Figure 1. Vagal oesophageal nociceptors, but not tension receptors (low threshold mechanosensors), discriminate innocuous and noxious levels of oesophageal distention. (*A*) Extracellular recordings were made from the vagal sensory neurones in nodose and jugular ganglia with mechanosensitive nerve terminals in oesophagus in the guinea pig isolated innervated oesophagus preparation. Both nodose and jugular ganglia supply nocieptors to oesophagus, while tension receptors are derived exclusively from nodose ganglion. Note that in the guinea pig (and larger mammals) the vagal nodose and jugular ganglia are readily identified as separated structures. In some mammals, such as rat and mouse, vagal sensory ganglia can fuse into a single elongated structure perhaps best described as a jugular/nodose complex. IX, X, XI and XII – glossopharyngeal, vagus, accessory and hypoglossal nerves, respectively. (*B*) Distention pressure-activity curves of vagal sensory nerve fibres in oesophagus. Distention of proximal gut > 60 mmHg is reported to cause responses consistent with pain in rodents. Note that the activity of tension receptors, but not nociceptors, saturates at presumably innocuous pressures. Vagal oesophageal nociceptors, but not tension receptors, express the capsaicin receptor TRPV1 that confers sensitivity to a variety of noxious chemical stimuli (not shown).

It has long been recognized that airways and lungs receive large numbers of vagal afferent C-fibres (often termed bronchopulmonary C-fibres) (Coleridge & Coleridge, 1984). These nerves nicely fit into Sherrington's definition of nociceptors. They are quiet during normal activity of the respiratory system but respond vigorously to a long list of noxious stimuli with, again using Sherrington's words, 'the common feature of having a nocuous character'. These stimuli include noxious airborne irritants, inflammatory mediators, and excessive tissue distension. The bronchopulmonary C-fibres, like the somatosensory nociceptors in skin, express the capsaicin receptor TRPV1, rendering them also sensitive to a variety of noxious chemical stimuli including vanilloids and acid. In addition, although bronchopulmonary nociceptors may not mediate pain, their activation has been associated with unpleasant sensations such as dyspnoea and can lead directly to protective reflexes that include apnoea, cough and mucus hypersecretion (Coleridge & Coleridge, 1984).

Textbooks and review articles often associate vagal afferent nerves in the oesophagus exclusively with the

autonomic regulation of homeostasis. This implies that the afferent nerves designed to respond to actual or impending tissue damage are limited to the spinal nerves with their cell bodies in the dorsal root ganglia. This hypothesis finds credence in studies where few, if any, vagal sensory nerve fibres in the oesophagus had characteristics consistent with nociceptors (e.g. Sengupta *et al.* 1989).

It has been recognized that noxious stimuli in oesophagus can amplify vagal reflexes such as cough. This and certain similarities in the pattern of the vagal innervation between lungs and oesophagus led us to hypothesize that the vagus supplies nociceptors to the oesophagus in a fashion similar to the bronchopulmonary C-fibres in the neighboring respiratory tract. Our recent paper experimentally addresses this hypothesis in guinea pigs (Yu *et al.* 2005).

We found that the guinea pig oesophagus is indeed supplied by a large population of vagal nociceptors. In fact, based on functional and histological assessment, nociceptive nerves may represent the predominant type of vagal afferent nerve in the oesophagus. The vagal nociceptors are readily distinguishable from vagal non-nociceptive low threshold mechanosensors (also termed tension receptors). Like spinal nociceptors, but unlike vagal tension receptors, vagal nociceptors discriminate noxious distension of the oesophagus (Fig. 1) and they express the TRPV1 receptor that confers sensitivity to variety of noxious chemical stimuli. Moreover, we found that vagal nociceptors in the oesophagus are not a homogeneous population, but can be divided into two groups based on their embryonic origin. Nociceptors derived from the embryonic placodes, whose cell bodies are situated in the vagal nodose ganglia, can be activated by a broad spectrum of autacoids, including 5-HT, ATP, and adenosine. Oesophageal vagal nociceptors derived from the neural crest, whose cell bodies are located in vagal jugular (supranodose) ganglia, are rather unresponsive to these autacoids. Placodes- and neural crest-derived vagal oesophageal nociceptors also differ in their expression of neurokinin peptides. The spinal afferent nerves innervating the oesophagus, many of which are nociceptors, also originate from neural crest. Based on some preliminary data, we speculate that their phenotype will prove to be more similar to jugular than to nodose vagal nociceptors.

Although it seems clear that the vagus nerves innervating the oesophagus comprise large numbers of nociceptors, the consequence of their activation is less clear. It can be reasoned that these nerves should cause effects consistent with the oesophagus 'being informed of its own injury'. Some recent work indicates that vagal afferent fibres are required for aversive responses to noxious gastric stimulation in the rat (Lamb *et al.* 2003). There has been speculation that vagal nociceptors may contribute to the emotional components that accompany pain perceptions (Berthoud & Neuhuber 2000). It is also likely that vagal nociceptors may serve to coordinate defensive reflexes aimed at diluting or ridding the tissue of the potential noxious stimuli.

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Noticeboard

Notices for the Summer 2006 issue of *Physiology News* should reach the Publications Office by **21 April**. Please send contributions to lrimmer@physoc.org.

Noticeboard

SOCIETY MEETINGS

For a full list of Physiological Society Meetings during 2006, see the tear-out Meeting card on p. 48 or visit http://www.physoc.org

2007

Glasgow, Scotland (*8-12 July*). Joint Meeting of The Physiological Society, Biochemical Society and British Pharmacological Society.

Bratislava, Slovakia (*10-14 September*). Joint Meeting of The Physiological Society, the Slovakian Physiological Society and FEPS.

International Workshops

Margarita Island (*19-24 March 2006*). *Membrane transport in health and disease.*

Kiev, Ukraine (*4-7 June 2006*). *The study of nociception from periphery to brainstem.*

Charles University, Prague (*21-23 September 2006*). *Lung function in health and disease.*

Full details at http://www.physoc.org/international/

EXPERIMENTAL BIOLOGY 2006

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

FEDERATION OF EUROPEAN NEUROSCIENCE SOCIETIES

Vienna, Austria (8-12 July 2006)
http://www.fens.org

8th INTERNATIONAL SYMPOSIUM ON NEUROBIOLOGY AND NEUROENDOCRINOLOGY OF AGING

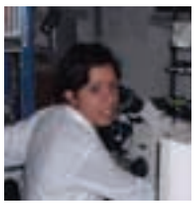
Bregenz, Austria (23-28 July 2006)
For the current list of speakers and other information visit http://www.neurobiology-and-neuroendocrinology-of-aging.org or contact Andrzej Bartke (abartke@siumed.edu) or Richard E Falvo (rfalvo@med.unc.edu).

IUPS

Kyoto, Japan (27 July-1 August 2009)
UK (July 2013)
http://www.iups.org

Calcium signalizing in developing mouse skeletal muscle fibres

Mice are born immobile and develop the ability to move over the first 2-3 weeks of life. Here Carlo Caputo and co-workers explore the underlying processes in skeletal muscle



Clockwise from above left: Joana Capote, Pura Bolaños and Carlo Caputo

Recently-born mice lack the capacity for movement, which is slowly acquired during the 2-3 weeks following birth. During this period, important changes take place at level of the molecular entities, schematically listed in Fig. 1, responsible for the series of events that start with membrane excitation and lead to massive calcium release and contractile activation in skeletal muscle fibres (Capote *et al.* 2005).

The records in Fig. 2 compare Ca^{2+} transients obtained with enzymatically dissociated flexor digitorum brevis muscle fibres from 7 and 42 day old mice, respectively. In adult animals the time course of Ca^{2+} transient is characterized by a fast rising phase, completed in about 1.5 ms, followed by a bi-exponential decay phase, with time constants of about 2 and 16 ms respectively. In 7 day old mice, the magnitude of Ca^{2+} transients is about one third while the raising phase of the transients is double that in adult fibres, while the bi-exponential decay phase is much slower, with time constants of 5 and 105 ms respectively.

Ca^{2+} currents in recently- born mice (Beam & Knudson, 1988) appear to contribute more to Ca^{2+} signalizing than in adult animals; thus in the absence of external Ca^{2+} the transient amplitude is diminished by 25% in the former and by 11% in the latter.

In principle the prolonged duration of the Ca^{2+} transients in young animals could be due to prolonged duration of action potentials caused by incomplete development of the K^+ delayed rectifier and by the presence of Ca^{2+} currents. However, optical measurements with the potentiometric dye Di-8-ANEPPS indicate that the duration of action potential is practically the same in young and adult fibres, precluding this possibility.

Alternatively, the slow decay of Ca^{2+} transients in young fibres could be attributed to poor development of the Ca^{2+} clearance mechanisms. The two components of the transient decay,

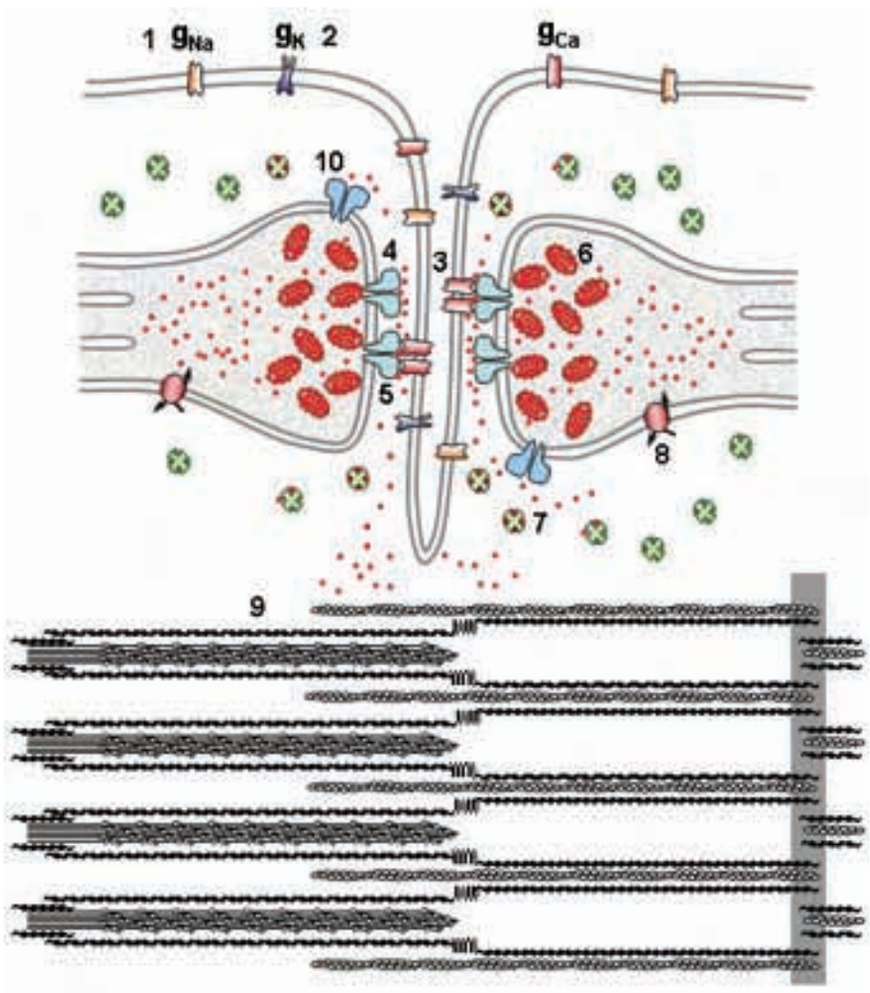


Figure 1. A schematic representation of the elements involved in Excitation-Contraction Coupling, (ECC). These comprise: Na and K channels responsible for membrane excitability (1,2). L-type Ca^{2+} channels, identified as dihydropyridine receptors (DHPr), that serve as voltage sensors for ECC and are disposed in tetrads in the t-tubule membrane (3). This DHPr together with RyR (4) that are Ca^{2+} release channels located in the SR membrane, may form Ca^{2+} release units (5) at the junctional region between the TT and SR membrane system. Calsequestrin (6), present in the SR lumen, controls the intraluminal Ca^{2+} concentration. PV (7) present in the myoplasm, serves as a fast Ca^{2+} buffer, with high affinity and relatively low capacity, binding Ca^{2+} at two sites normally occupied by Mg. Ca^{2+}-ATPase present in the SR membrane (8), with high capacity for Ca^{2+} is responsible for maintaining a low intracellular $[Ca^{2+}]_i$, and together with PV is responsible for Ca^{2+} clearance after contractile activation. The contractile machinery formed by different proteins (9). Notice that non-junctional RyR (10) may also be present in the SR membrane.
All these elements are not completely developed at the moment of birth. The isoform RyR3 is present at the moment of birth and markedly diminishes during the first two weeks. PV is almost absent at birth and starts increasing after birth.

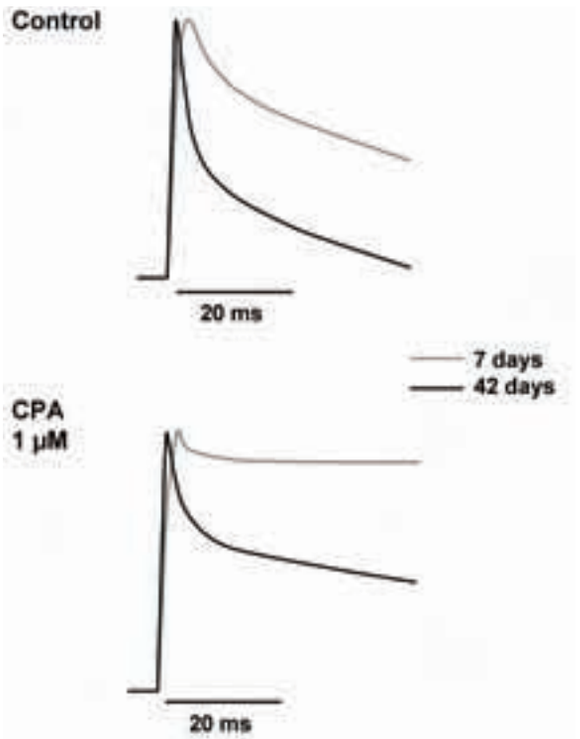


Figure 2. Comparison of Ca^{2+} transients in fibres from young and mature mice. The upper records compare Ca^{2+} transients in two fibres from 7 and 43 days old animals, respectively. The records have been scaled to better show the difference in their time courses. The lower records show a similar comparison after poisoning the fibres with cyclopiazonic acid to block the SR Ca^{2+} ATPase activity.

characterized by the two time constants, could be associated with the operation of the myoplasmic Ca^{2+}-sequestering protein parvalbumin (PV) and of the sarcoplasmic reticulum (SR) Ca^{2+} ATPase activity respectively. Poisoning of the SERCA pump by cyclopiazonic acid reveals the presence of an initial, fast, poison insensitive recapture component in adult, which is much reduced in young animals. This is consistent with the notion that PV content is very low at birth and increases during postnatal development (Leberer & Pette, 1986).

Interestingly, robust Ca^{2+} transients appear in muscle fibres early after birth (6-7 days) indicating that at this time the mechanisms underlying ECC are sufficiently developed to produce sizeable Ca^{2+} release. This is even though the Ca^{2+} release units formed by ryanodine (RyR) and dihydropyridine receptors (DHPr) at the level of the junctional region between T-tubules (TT) and SR are completed only 2 or 3 weeks after birth (Franzini-Armstrong, 1991).

In spite of robust Ca^{2+} release, motility is much reduced and slow in young animals (Close, 1964), indicating that the development of the contractile apparatus is the limiting factor. The slowness of movement in young animals may be caused by a poorly developed Ca^{2+} uptake systems, both PV and SR Ca^{2+} ATPase, and also by the the fact that the myosin isoform in young animals is of the slow muscle type (Whalen *et al*. 1981). Thus it is clear that the capacity to develop Ca^{2+} transients is acquired prior to the complete development of structures involved in contractile activation, in particular myofibrils. This in turn indicates that Ca^{2+} signals may have a role in myofibrillogenesis (Li *et al*. 2005).

Acknowledgement

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Memorable Members

G L Brown (pictured above) died over 30 years ago, but his name remains familiar to physiologists of all ages in the UK and RoI. He is commemorated annually in the G L Brown Lectures that The Society established in 1975. Those of us lucky enough to have met him need no reminder of his ebullient character. Stories about him, some printable, some not, are legion.

Two examples concern David Whitteridge who succeeded him as Waynefleet Professor in Oxford. David was another of The Society's greats who, though he mellowed much with age, had a reputation for acerbity. This led G L to describe him as the physiologist with the highest IQ and the lowest pH. At my first ever Phys Soc Meeting (Edinburgh 1952), Whitteridge mentioned in a discussion that Paintal had evidence for a cast iron ventricular baroreceptor afferent fibre. 'Oh', said G L 'Perhaps Professor Whitteridge would care to tell us the conduction velocity in cast iron.'

Ann Silver

The 2006/7 G L Brown Prize Lectures have been awarded to C A R Boyd (see p. 38).

A racing start for the heart in exercise

At the onset of exercise the heart rate changes within one second to bring about a 25% increase in the heart rate, but what initiates these changes? Valerie Gladwell takes a closer look at the mechanisms involved, focusing on how feedback from the muscle alters the heart rate via cardiac vagal activity

The brain's command to exercising skeletal muscles undoubtedly simultaneously initiates appropriate cardiovascular changes (Secher, 1999). However, feedback from the contracting muscles also contributes significantly. Recent data suggest a special role for one type of afferent fibre in inhibiting cardiac vagal activity.

Studies in animals show that stimulation of the small afferent nerve fibres within the muscle cause increases in heart rate and blood pressure (Coote *et al*. 1971). Similar effects have been shown in humans with electrical stimulation to induce muscle contraction. This evokes changes in heart rate and blood pressure of a similar magnitude to those contractions which are voluntary in nature. Furthermore, when circulation is occluded at the end of involuntary contraction, blood pressure remains elevated, whereas heart rate falls rapidly to baseline levels (Bull *et al.* 1989). (Fig. 1).

Two types of slow conducting muscle afferent fibres (type III and IV) have been shown to contribute to the cardiovascular changes via feedback mechanisms; type IV have been shown in humans and animals to respond to accumulation of metabolites, whereas type III respond to mechanical stimuli. It is likely that there is some overlap between these receptors with some responding to both types of stimuli. As heart rate increases rapidly at the initiation of contraction and rapidly falls to baseline at the end of contraction, particularly if metaboreceptors continue to be stimulated at the end of the contraction (by occlusion of the blood supply and thus trapping metabolites), it is unlikely that the metaboreceptors are the major contributing factor to the changes in heart rate. It is more probable that mechanoreceptor stimulation is responsible for the rapid rise at the initiation of contraction, with the removal of stimulation causing the fall in heart rate at the termination of contraction.

Valerie Gladwell

Although experiments have been conducted in animals to look at the selective influence of type III afferents, it has proved to be more difficult in humans. However, recent experiments in humans have been conducted to try to stimulate mechanoreceptors selectively. Leg compression to increase intramuscular pressure has been used and caused increases in both heart rate and blood pressure (Williamson *et al.* 1994). This stimulus is likely to stimulate both type III and IV afferents or polymodal afferents.

We considered that a 'purer' method of muscle mechanoreceptor stimulation would be to use sustained passive stretching of the muscle whilst the subject was in a semi-supine position (Gladwell & Coote, 2002). Heart rate increased rapidly and the increase was sustained during the stretching period, whilst there was only a transient increase in blood pressure. Additionally, it was identified that rhythmic passive stretching did not elicit any cardiovascular response, suggesting that larger afferent spindles and Golgi tendon organs did not play a role. Interestingly, the cardiovascular response to stretch performed following muscle contraction with occluded circulation was not sensitized by the metabolic conditions within the muscle. (Fisher *et al.* 2005).

In animal models, passive stretch of the muscle has been shown to elicit a reduction in cardiac vagal activity (Murata & Matsukawa, 2001). In humans, the increase in heart rate brought about by the stimulation of mechanoreceptors is also likely to be vagally-mediated, judged by the rapidity of the change and a decrease in heart rate variability, which is an index of vagal activity. Further, as animal experiments have shown that the baseline level of vagal activity is

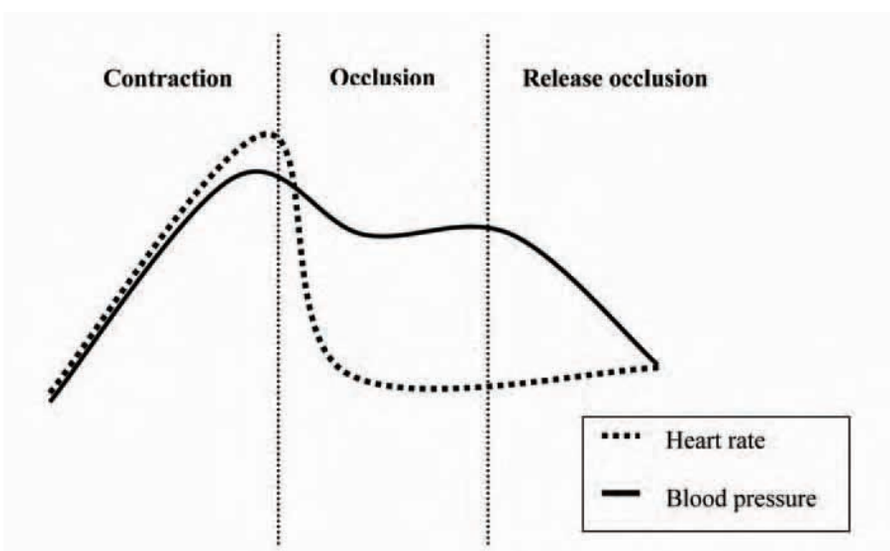

Figure 1. Schematic drawing showing heart rate changes (dashed line) and blood pressure changes (solid line) during contraction period and occlusion of the blood supply following isometric muscle contraction.

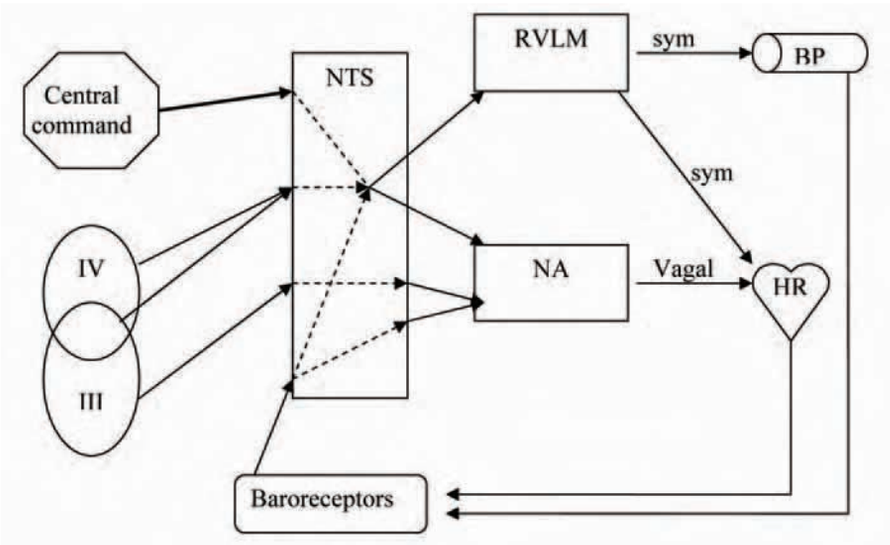

Figure 2. Factors controlling heart rate and blood pressure during exercise. It illustrates the mechanoreceptors (III, IV and Polymodal), baroreceptor and central command inputs and possible sites of interaction where arrows converge NTS= nucleus tractus solitarus; RVLM= rostroventrolateral medulla; NA =nucleus ambiguous.

important in the heart rate response to contraction, we performed additional experiments which altered the level of vagal activity just prior to the stretching period. Drug induced vagal blockade and rhythmic hand-grip, both of which reduce vagal activity, significantly decreased the response to passive stretch (Gladwell *et al.* 2005).

An additional way of altering vagal activity is to alter the input from the baroreceptors using brief pressure or suction over the baroreceptors which are located in the carotid sinus in the neck. An increase in pressure mimics a decrease in blood pressure, leading to a decrease in vagal activity, whereas suction mimics an increase in blood pressure causing an increase in vagal activity. Interestingly, neck suction which results in a decrease in heart rate significantly reduced the increase in heart rate caused by passive stretching. This suggests that the increase in vagal activity brought about by the neck suction is not overcome by the stimulation of the mechanoreceptors. It is likely that this indicates that the stimulation of the mechanoreceptors is not great enough to overcome the increase in cardiac vagal activity by the baroreceptor afferents. Neck pressure, on the other hand, resulted in a slight augmentation of the response to stretch. The results of both neck pressure and neck suction may provide additional evidence to support an argument that the two opposing inputs (mechanoreceptor and baroreceptor afferents) interact at a common neuronal pool.

Studies to date have shown that the stimulation of muscle afferents has a specific functional role in exercise, with mechanoreceptors (alongside central command) inducing the rapid increase in heart rate at the onset of exercise by a reduction in vagal activity (Fig. 2).

The mechanoreceptors that are probably responsible for this immediate reduction in vagal activity are likely to be those Group III afferent fibres that respond to stretch. We suggest that these could be called 'tentonoreceptors' (from the Greek 'tentono' meaning stretch) to distinguish them from other types of mechanoreceptors found elsewhere. The stimulation of these tentonoreceptors is likely to be important to ensure close matching of cardiac output and oxygen delivery to the exercising muscle in the early stages of exercise, prior to the re-distribution of blood flow.

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European Federation of Autonomic Societies

The 8th Meeting of the European Federation of Autonomic Societies (EFAS), *Physiology and physiopathology of the autonomic nervous system*, will take place at the Lisbon Faculty of Medicine, Lisbon, Portugal from 24-27 May 2006.

The main topics to be covered include:

- Parkinsonism
- Obesity
- Receptor dysfunction
- Autoimmune diseases
- Quantitative physiology
- Diabetes
- Sleep and disautonomy
- Hypertension
- Deposit diseases
- Neuro-ophthalmology
- Disorders and physiology of the autonomic nervous system

Full details available at http://www.efas2006.fm.ul.pt/

Light up the signal fires – imaging calcium's protein partners

In Victorian times, almost all microscopes sold came with an attachment to facilitate the observation of blood flow in the tail of a tadpole. Using this, the paterfamilias could demonstrate to his family the opaque red blood corpuscles coursing through otherwise invisible vessels that branched and anastomized. More advanced microscopists killed, fixed and stained the tadpole to reveal the various tissues in more or less detail.

Ten years ago our study of calcium signalling in cells was at a similar stage. Thanks to the indicator dyes created by Roger Tsien and others we could see where calcium ions accumulated, and the paths through which they moved through the cytoplasm. By killing and fixing the cell we could see its organelles and even the location of individual proteins – at the time of fixation – in exquisite detail. However, we could not watch the interaction between calcium and other components in a living cell. The development of green fluorescent protein and other novel live cell

Stephen Bolsover

imaging technologies has changed this situation dramatically. We can now see where particular proteins or organelles are in living cells, and watch how this pattern overlaps with, or changes in response to, calcium signals. The most advanced protein constructs go further and report not only their location but also their conformation.

The immediate targets of calcium are the calcium binding proteins, among which calmodulin dominates. Figure 1 shows two ways in which calcium and calmodulin can interact spatially. In nerve cell bodies calmodulin is distributed relatively uniformly (panel *A*) while electrical activity evokes a calcium signal that is largest at the cell periphery (*B*). In contrast, stimulation of mast cells releases calcium from intracellular stores causing a relatively uniform calcium increase (*E*), but calmodulin is concentrated at the periphery (*D*). Stimulation of both types of cell generates a high concentration of active calmodulin at the periphery, as revealed by imaging of a reporter calmodulin (*C*).

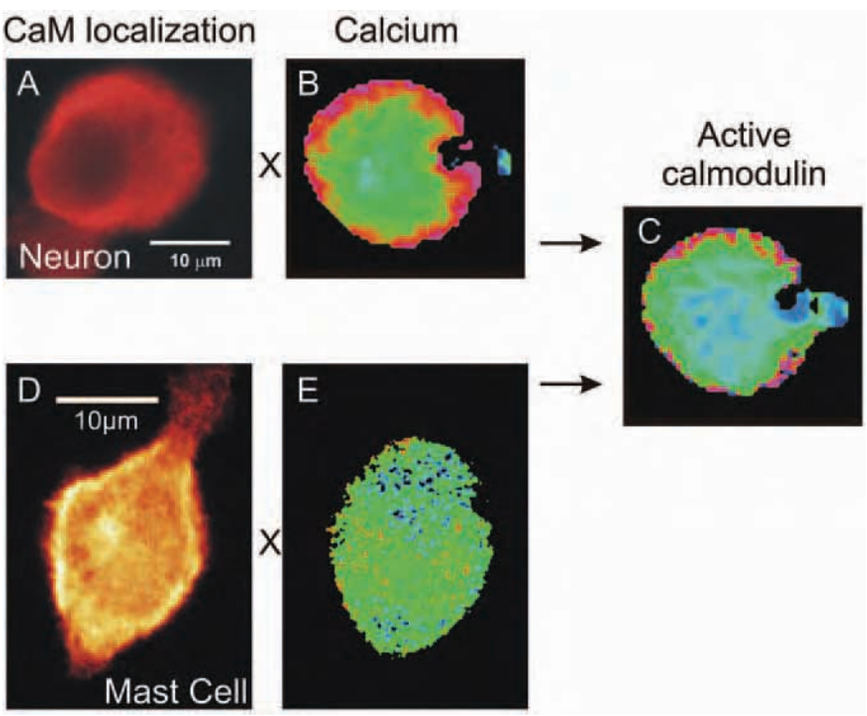

Figure 1. Two strategies to one end. *A-C*: rat sensory neurones showing respectively endogenous calmodulin (by immunofluorescence) then calcium and Ca:calmodulin concentrations after 200msec of voltage clamp depolarization. From (Milikan & Bolsover, 2000; Milikan *et al*. 2002). *D*, *E*: RBL cells showing respectively a calmodulin-GFP chimaera, and calcium after 30 seconds of stimulation.

Because the calcium transient and the spatial distribution of the target protein have to overlap for a response to be elicited, the system constitutes an 'and' gate. For example, the neurotransmitter glutamate will cause the calcium concentration to increase in the nuclei of hippocampal neurones, but this calcium increase can only activate the nuclear transcription factor CREB if calmodulin has previously been caused to move to the nucleus by electrical activity (Mermelstein *et al.* 2001).

The movement of calmodulin to the nucleus of electrically active neurons is one example of calcium-evoked translocation. The mechanisms that cause proteins to move in response to a calcium signal are many, and vary in complexity. Some proteins use calcium ions as part of the coupling that attaches them to a cellular location. A rise of calcium concentration in that cell region will therefore recruit the protein. Examples are protein kinase C (Fig. 2*A*, *B*) (Bolsover *et al.* 2003) and annexin. Other proteins are post-translationally modified in response to a calcium signal. Their subsequent movement need not, therefore, be dependent on where the calcium signal occurred. The transcription factor NFAT behaves in this way (Fig. 2*C*, *D*). It bears a nuclear localization signal that is only active when the protein is dephosphorylated by the calmodulin dependent phosphatase calcineurin (PP2B). Thus NFAT can be dephosphorylated at the location where calcium increases (assuming that calcineurin is present); its subsequent movement to the nucleus will be calcium-independent. Since the time

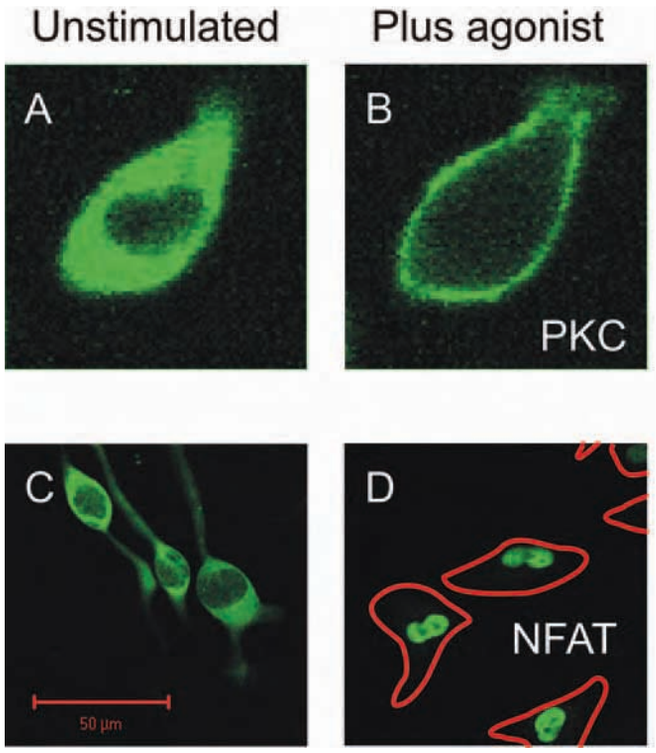

Figure 2. In RBL cells one calcium signal sends proteins to two distinct targets. *A*, *B*: the same cell expressing a PKCα-GFP chimaera before and after stimulation. *C*, *D*: populations of cells expressing a GFP-NFAT chimaera at rest and after stimulation respectively. Red in D indicates the otherwise invisible cell margins. From (Bolsover *et al*. 2003; Pandey *et al*. 2004).

constant of NFAT rephosphorylation is of the order of 7 minutes (Tomida *et al.* 2003), even low frequency calcium transients can cause a maintained NFAT translocation (Pandey *et al.* 2004).

With the help of GFP and other fluorescent labels, achieving our goal of mapping the interactions of calcium and its downstream targets in living cells is literally in sight.

Stephen Bolsover
Department of Physiology, University College London, UK

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2006 Prize Lectures

The Physiological Society has awarded the following Prize Lectures:

Mark Fishman (Annual Review Prize Lecture)
Mark J Dunne (Australian/UK Visiting Lectureship Scheme)
Rod Flower (Bayliss-Starling Prize Lecture)
Matthew Bailey (Biller Prize Lecture)
C A Richard Boyd (G L Brown Prize Lectures*)
Thomas Jentsch (Hodgkin-Huxley-Katz Prize Lecture)
Susan Wray (Joan Mott Prize Lecture)
Neville McClenghan (Sharpey-Schafer Lecture and Prize)
Helen Kennedy (Wellcome Prize Lecture)

* See *G L Brown – a memorable Member (p. 34)*

A Murray Harper

1933-2005

For 25 years from the mid 1960s, the elucidation of the physiology of cerebral blood flow owed more to Murray Harper than to any other investigator in Britain or, indeed, internationally. As a medical graduate in Glasgow, he developed a particular interest in brain blood flow in the context of cardio-pulmonary bypass, and he was to become leader of a research team in laboratories established for the purpose at the Wellcome Surgical Institute, University of Glasgow where Murray was ultimately Professor of Surgical Physiology. He pioneered radioactive inert gas methods for brain blood flow measurement and, from his MD thesis in the 1960s onwards, his publications developed the concept of the local regulation of the smaller brain blood vessels by metabolic and chemical rather than neural control. His definition of the influence of sympathetic nerves on brain blood flow and the interplay between blood pressure and carbon dioxide tension are seminal contributions. Murray championed multidisciplinary research and, although he focused on basic research, he was also actively involved in human studies along with neurosurgeons, anaesthetists and clinical physicists. He was one of the founders of the International Society of Cerebral Blood Flow and Metabolism and was the first editor of its journal. In 1987 we were privileged to arrange with him a symposium on this topic at a Physiological Society Meeting in Glasgow, with later publication of the proceedings as a Study Guide. He was indeed a physiologist of major international and historical significance.

Sheila Jennett
James McCulloch

The Society's 'mascot'

Through the magic of the World Wide Web I have been reading with great interest the article in *Physiology News* (**60**, 37)) about the loss and recasting of The Society's 'mascot' – the little dog.

I am the Brian Blood (bass recorder player rather than tenor) who was a research student with Denis Noble and who arranged, through the good offices of my wife (Marguerite Dolmetsch) and the Dolmetsch family musical instrument making company, the turning of the circular plinth to which the dog was to be attached.

If my memory serves me right, the circular stand was made in 1976 the year of the centenary celebrations of The Society which culminated in a dinner in Trinity College, Cambridge.

We were asked to make this new plinth because the dog tended to fall off the Victorian stand on which it only rested.

Your photographs are therefore confusing. We did not make the Victorian stand which is shown at the top of column two on page 37 but we did make the base that is just visible in the picture (above) taken from R Chapman's article in the 1994 *Physiological Society Magazine*.

The Dolmetsch business founded in 1883 continues to flourish in Haslemere, Surrey and Members interested in our history are invited to visit our web site www.dolmetsch.com

Brian Blood
Dolmetsch Music Instruments, Haslemere, Surrey, UK

Editorial note: Our sincere apologies to Brian Blood for misrepresenting the work of Dolmetsch Musical Instruments

Stem cell rush

Congratulations to J Prakasa Rao (*Physiology News* **61**, 42) for having the guts to point out the folly of the lemming-like rush to stem cell technology! The UK Stem Cell Initiative has been lobbying very effectively for this bandwagon. Between £650m and £820m will be invested over the next 10 years, and total public sector funding for stem cell research over the 2 year period 2006 to 2008 is now up to £100m.

Part of the excitement is because restrictions on the use of stem cells in the US make this one of the few fields in which the UK can compete – if we don't get overtaken by Korea, Spain, Israel, etc.

It would be funny if it were not for the fact that research funds from all sources are being diverted into this area at the expense of worthwhile science that has more immediate prospects of conferring therapeutic benefit.

Stanley Salmons
Department of Human Anatomy & Cell Biology, University of Liverpool , UK

Nobel Prize 2005

Rather than look to a basic research discovery, the 2005 Nobel Prize Committee for Physiology or Medicine honoured what the *British Medical Journal* described as 'old-fashioned medical detective work' by awarding the Nobel to two Australians, pathologist Robin Warren and gastroenterologist Barry Marshall, of the University of Western Australia in Perth. Their achievement was to discover (or rediscover) the stomach-dwelling bacterium *Helicobacter Pylori* and to recognise the link between infections with *H Pylori* and inflammation of the stomach lining (gastritis) leading to ulcers (Marshall & Warren, 1984). This insight has led directly to the successful medical treatment of ulcers with antibiotic regimes. Previously, the many patients with troublesome ulcers had little option for a 'cure' other than surgical vagotomy or even gastrectomy, drastic solutions which were nonetheless widely practised well into the late 1980s.

Many of the reports on Marshall and Warren's Prize have rightly emphasised the struggle they had to get their observation of bacteria in the gastric mucosa accepted through the 1980s. As Warren notes in his Nobel lecture (Warren, 2005), the observation of such bacteria in stomach sections was at least a hundred years old when they started their work, and had been 're-discovered' periodically (see Marshall, 2002). However, the dominant consensus in the early 1980s was that the stomach lumen was sterile, due to its acidity, and that no bacteria could grow there.

The difficulty the two had getting their ideas accepted ultimately led Marshall to undertake a celebrated self-experiment where he drank an *H Pylori* culture to give himself acute gastritis, which was subsequently cured with antibiotic therapy. Another widely-reported facet of the story was the serendipitous way in which the culture conditions for successfully growing *H Pylori* were arrived at. They had been culturing gastric biopsy specimens for the standard 48 h, but the 1982 Easter weekend, and/or an epidemic of MRSA at the Royal Perth Hospital which backed up the pathology labs, meant that one sample was left for over 5 days before being examined. Unlike the samples examined and thrown out after 48 h, when bacterial

growth was scarce to invisible, the 'old' specimen showed an abundant growth of the (slow-growing) *H Pylori*. In fact, up to 50% of humans are colonized with *H Pylori*, typically being infected in early childhood, although most people have no symptoms of the bacterium's presence. *H Pylori* is able to induce multiples changes, including proliferation, in gastric epithelium, and is a key factor in the development of many gastric cancers. Much research now focuses on why only some people who are infected develop the severe changes in mucosal (patho) physiology that lead to cancer and ulcers.

So what lessons are there for physiologists in the story? Perhaps the main one is that the normal, as well as abnormal, physiology of an epithelium may actually involve co-resident microorganisms. This emphasises the topicality of symposia like that on *Epithelia-Microbe Interactions* held a couple of years ago in Newcastle.

Another lesson is the timeless one of not letting one's scientific curiosity be blinded by an apparent consensus. Barry Marshall's Nobel lecture (Marshall, 2005) quotes the historian David Boorstein: 'The greatest obstacle to knowledge is not ignorance – it is the illusion of knowledge'.

Austin Elliott

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Warren JR. http://nobelprize.org/medicine/laureates/2005/warren-lecture.html

I'm a leading scientist – get me out of here

Science is often accused of being inaccessible to the general public. Scientists counter that this is because scientists don't get enough media exposure. This includes both real scientists, and people playing scientists in TV dramas. We can all agree that there are less TV shows with scientists in them than shows about policemen, or doctors.

But I think I have come up with a solution. Since the public's appetite for reality TV seems to be insatiable, let's give them what they want AND get ourselves some much-needed exposure.

I give you: *Celebrity Scientist Big Brother*

The beauty of this is that this idea can be franchised; you could have different versions for different scientific disciplines, or one for just your own Department, or a national all-star version, or an international one. The possibilities are endless.

There are, however, some easy rules to enable you to select the contestants for maximum viewing figures. The people inhabiting the house/jungle/island should include:

• at least one person recently dramatically publicly disgraced and in search of rehabilitation

• a person who has undergone extensive cosmetic surgery or dental work

• a minor member of the aristocracy, or a Lord, Sir or Right Hon

• one person who is faking the whole thing

• one or more relentless self-publicists

• one or more people who are extensively tattoo-ed, and/or pierced in improbable places [May be difficult to fill this role with scientists, but you never know]

• one monosyllabic youth person given to mumbling 'Yeh, wicked' at random intervals [male PhD students are the obvious candidates here]

• one or more people who are pathologically argumentative

• one person teetering on the edge of a public mini-nervous breakdown [Given the proximity of RAE2008 any Head of Department or RAE2008 Submission Task-force Leader should be a good bet]

• at least one person who even the other contestants find weird and unsettling

• one person who you thought would never be seen dead on a show like this. This person should subsequently storm out in a cloud of invective and denunciations (think Germaine Greer or Johnny Rotten)

• several people who used to be vaguely well-known, typically for having once appeared on television, but have now largely faded from view.

This mix should ensure plenty of good reality TV, including shouting, swearing arguments, tears and perhaps even a fight or two.

Of course, some contestants may fulfil several of the above criteria at the same time. If so, so much the better.

Finally, all the participants need to share some basic personality traits. They should be able to talk tirelessly about themselves and their work until the small hours, and should believe unquestioningly that their merest utterance is deeply fascinating and demands the rapt attention of all those listening.

'They'll all be professors, then' commented a friend on hearing this.

Hmmm. You might think that.

I couldn't possibly comment.

Mark Cain

THE JOURNAL OF PHYSIOLOGY

New for 2006

Nine new sections now appear on the back cover and contents page of *The Journal of Physiology* in place of the previous four:

- **Molecular and genomic**
- **Cellular**
- **Neuroscience**
- **Cardiovascular**
- **Alimentary**
- **Renal and endocrine**
- **Respiratory**
- **Skeletal muscle and exercise**
- **Integrative**

Pdf files of published papers and pre-publication manuscripts from the web site now include a front and back cover with branding.

The copyright line at the bottom of the page now acknowledges the authors rather than The Society as holding the copyright. *The Journal*'s Exclusive Licence Form[1] should be consulted for full details, but rights to publication of reviewed and copy-edited articles are assigned to Blackwell Publishing, acting on behalf of The Society. The final *Journal of Physiology* pdf cannot be posted online by the authors at any time. Authors may only make their own manuscript available online for the period before acceptance and from one year after final print publication: it cannot be made available by the authors during the one year period when there is no free access to the final paper at *The Journal*'s own web site.

The cost to authors of **colour figures** in research papers is now lower – £200 for the first figure and £60 for each subsequent figure. As previously, online-only colour figures and colour figures in Topical Reviews and Symposium Reports are free.

The Journal of Physiology symposia

Involvement of interstitial cells of Cajal in the control of smooth muscle excitability

Saturday, 22 July 2006

at the Japanese Society for Smooth Muscle Research, Okayama, Japan

For further information go to http://jp.physoc.org

In the news

A paper published in volume 569.2 of *The Journal of Physiology* by Combaret *et al*. (2005), together with a Perspective by Michael Rennie, received wide media coverage following a pilot project by *The Journal*'s Executive Committee to promote suitable papers in this way. Among the coverage received, the BBC produced a well-informed report of the research and its relevance to the general public, namely that older people should keep eating protein in order to maintain their muscle mass. Promotion in the press of papers that have clear relevance to human health not only raises the profile of The Society's journals, but also helps to fulfil the mission of The Society to 'contribute to the progress and understanding of biomedical and related sciences and the detection, prevention and treatment of disease, disability and malfunction of physical processes in all forms of life'.

Combaret L, Dardevet D, Rieu I, Pouch M-N, Bechet D, Taillandier D, Grizard J & Attaix D (2005). A leucine-supplemented diet restores the defective postprandial inhibition of proteasome-dependent proteolysis in aged rat skeletal muscle. *J Physiol* **569**, 489-499.

Archives

The NLM/Wellcome Trust archiving project is on track and it is hoped that all articles published in *The Journal* from 1878 will be available online at PubMed by May.

Letters

In addition to Perspectives and Classical Perspectives, Letters to the Editor and the focus articles of Perspectives will be made freely available online and identified using 'free article' icons.

Special Issues

A number of Special Issues of *The Journal* are planned for 2006. These include:

- **AMP kinase: metabolic sensing in health and disease**
- **The mammalian transcriptome and the cellular complexity of the brain**
- **The cochlea**

There will be a call for related papers ahead of each Special Issue.

Wellcome Trust funded research

Wellcome Trust funded researchers are reminded that they can publish in *The Journal of Physiology* and *Experimental Physiology*.

The Wellcome Trust requires electronic copies of any research papers that have been accepted for publication in a peer-reviewed journal, and are supported in whole or in part by Wellcome Trust funding, to be deposited at PubMed Central (or UK PubMed Central once established).

This requirement will apply to all grants awarded after 1 October 2005 and, from 1 October 2006, to all grants regardless of award date. The Trust will provide grant holders with additional funding to cover the costs of open access publishing so that they can post their articles on PubMed Central immediately on publication. This funding will be provided for articles reporting research that was part-funded by the Wellcome Trust.

Both journals offer authors an open access publishing option through Blackwell Publishing's Online Open service.[2]

To apply for funding to make your paper in The Society's journals open access through Online Open, please contact your institution's Research Office or The Physiological Society Publications Office for advice. (journals@physoc.org).

Carol Huxley
Managing Editor

[1]http://www.blackwellpublishing.com/pdf/tjp_caf.pdf
[2]http://www.blackwellpublishing.com/static/onlineopen.asp

Experimental Physiology
Translation & Integration

The rise of *Experimental Physiology*

The journal started by Sharpey Schafer in 1908 continues to play an important role in communicating scientific discoveries to a world-wide audience. In 2005 its recent upward progress has been maintained with a further rise in impact factor to 1.88, and this when most other physiological-type journals declined. An increasing world-wide readership can be attributed to its mixture of popular content, including:

- **Hot Topic reviews**
featuring articles pertinent to the heart, the circulation and the brain
- **Prize Lectures**
covering respiratory control, exercise and metabolism, and tissue engineering
- **Review articles**
on the latest developments in non-invasive measurement of blood pressure and stroke volume
- **Exchange of Views articles**
which, in the latest issue, feature differing views on central chemoreceptors.

Part of our mission to publish papers ascribing physiological function to genes and proteins in the context of integrative systems has been met by themed sections, one on aspects of cardiovascular genomics and another on the use of viral vectors in neuroscience. Translational and integrative physiology has also been highlighted in three symposia with published articles covering *Heart-kidney interaction, Structure of blood vessels* and a third on *Obesity-related hypertension.* This focus was continued in the 67 original research papers also published in the six issues of 2005. This year there will be Themed Issues on *Cardiovascular aspects of exercise* and *Computational modelling in physiology*. In July 2006 I step down as Chair of the Editorial Board. David Paterson has been elected to replace me, whilst Julian Paton becomes Deputy Chair. These two, together with Nadurai Prabhakar, our USA Deputy Chair, represent a formidable team which will ensure the continued progress of the journal through its centenary year in 2008. I wish them well and hope that Members of The Society will maintain their whole-hearted support for the journal.

John H Coote

Themed Issue – Modelling of biological systems

The March issue of *Experimental Physiology* (Vol 91. 2) develops the translation and integration theme of the journal by presenting a Themed Issue on ***Modelling of biological systems***. The issue is edited by David Paterson (Chair of the Editorial Board from July), Andrew McCulloch and Peter Hunter. Contributing authors include Chris Bradley, Martin Buist, Kelly Burrowes, Neil Cherniack, Richard Clayton, Justin Fernandez, Martin Hayward, Eric Hoffman, Darren Hooks, Panny Kallis, Peter Kohl, Ian LeGrice, Guy Longobardo, Martyn Nash, Peter Taggart, Natalia Trayanova, Marcus Pandy, Andrew Pullan, Bruce Smaill, Peter Sutton, Merryn Tawhai and Mark Trew.

Nearly all of the papers in the Themed Issue describe mathematical models of organs or organ systems based on biophysical equations solved on three-dimensional (3D) finite element representations of the organ anatomy. The finite element method is a computational technique that is widely applied in the analysis of complex engineering structures but is equally applicable to modelling the complex anatomy of organ systems and the anisotropic, inhomogeneous and highly nonlinear properties of biological tissues. The organ systems considered in this Themed Issue are the heart, the lungs, the digestive system and the musculo-skeletal system.

Many of the papers have a clinical focus. Fernandez and Pandy, for example, propose a framework for incorporating lower limb gait analysis data, ground reaction force data and EMG data into subject specific models of walking based on solving the equations of continuum mechanics on models that incorporate the 3D anatomy of the major muscle groups of the leg. The paper by Buist *et al*. links gastric slow wave activity on anatomically-based models of the stomach to clinical measurements of the electromagnetic fields produced by these waves under conditions of cellular uncoupling induced by ischaemia.

Tawhai *et al*. consider structure-function relations in the pulmonary circulation within the context of a 3D anatomical model of the lungs that was illustrated on the cover of the inaugural issue of the new *Experimental Physiology* launched in January 2004 (Crampin *et al*. 2004). The model

Experimental Physiology is delighted to announce the appointment of Paul Flecknell as an adviser to the Editorial Board..

Paul (pictured right) writes:

'My research interests are the welfare of animals used in biomedical research and, in particular, issues associated with pain and distress. I am also interested in comparative aspects of pain assessment and allevation, animal anaesthesia and the neurophysiological effects of anaesthetics. Current research projects aim to develop methods of pain assessment and alleviation for use in animals and in human neonates. My group is also investigating neurophysiological effects of anaesthesia, and assessing methods of euthanasia of rodents. We also disseminate our research results by developing training materials for research workers (http://www.digires.co.uk and http:www.ahwla.org.uk).

I graduated from Cambridge in 1976, and started my career as a clinical veterinarian at the University of Bristol. I became involved in medical research at the MRC Clinical Research Centre in London, while acting as their laboratory animal veterinarian. After completing a PhD in physiology, I moved to Newcastle where I was able to develop my major interests in the science underpinning animal welfare. I am responsible for the overall management of the university research animal facilities and I am also the University's 'Named Veterinary Surgeon'. I head a research group whose main objectives are strongly linked to improving the welfare of laboratory animals.'

predicts the patterns of perfusion in response to different lung orientiations under gravity loading for both normal and diseased conditions. A different approach to modelling the lung is taken by Cherniack and Longobardo, who use a control theory model to examine the role of periodic breathing in understanding cardiovascular and respiratory disorders.

Another important theme of *Experimental Physiology* is integration via multi-scale models – these are models that represent molecular events within the context of solving biophysical equations at the tissue level. Four examples of this in the March Themed issue are the incorporation of models of ion channel electrophysiology in cardiac tissue simulations by Kohl *et al*. (the role of mechanically sensitive ion channels), Trayanova (mechanisms of defibrillation), Nash *et al*. (action potential restitution properties of cardiac tissue) and Trew *et al*. (the role of cardiac tissue structure in electrical wave propagation). The approach to modelling heart physiology with cell level processes incorporated into the physical equations governing function at the tissue and whole organ level owes much to the pioneering cardiac ion channel modelling work by Denis Noble in the UK (Noble, 2002).

This Themed issue can be seen as representative of a major new direction in physiology that holds considerable promise for integrating experimental data at the protein, cell and tissue levels into whole organ function.

Peter Hunter
Bioengineering Institute, University of Auckland, New Zealand

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Crampin, EJ, Halstead M, Hunter P, Nielsen P, Noble D, Smith N & Tawhai M (2004). Computational physiology and the physiome project, Experimental Physiology 89, 1-26,

Noble D (2002). Modeling the heart: from genes to cells to the whole organ. *Science* **295**, 1678-1682.

Changes to The Physiological Society and publication of The Proceedings

Informal discussion with Members of The Society suggests that many are not fully aware of the changes that have happened to The Society over the last few years. These include the governance changes and, with regard to our Scientific Meetings, the move to an Annual Main Meeting plus Focused Meetings. Information on pages 47-48 aims to address some of these uncertainties. The page is designed to be removed and posted somewhere convenient.

Members should also be aware of changes to the publication of the Proceedings of our Scientific Meetings. Meetings abstracts are no longer published as part of *The Journal of Physiology* but will form a separate online-only publication entitled *Proceedings of The Physiological Society*. Volume 1 will comprise the abstracts from the Focused Meeting held in December 2005 at University College London. Citations will be in the following format:

Smith A & Jones B (2006). *Proc Physiol Soc* **1**, C53.

In practice, the change will make very little difference. *The Proceedings* will continue to be hosted on The Society's web site, and there will still be a link from *The Journal* home page; they remain accessible via search engines. As meetings abstracts, *The Proceedings* will not be listed in ISI (they have not been since 2003 when they went online only).

Free EP archive 1908-2004

Back copies of *Experimental Physiology* from 1908 to 2004 are now freely accessible at
http://ep.physoc.org/contents-by-date.0.shtml
The archive contains searchable pdf files of all manuscripts and material published in *The Quarterly Journal of Experimental Physiology* 1908-1989 and *Experimental Physiology* from 1990.

Where are all the women going?

New Affiliate representative Patricia de Winter ponders the increasing popularity of scientific writing as a career choice

I was rather surprised to be asked to replace Laura Blackburn as the Affiliate representative on the *Physiology News* group, as I currently serve on The Society's Council and thought that there might be some conflict. However, when I was reassured that there was none, I realised that this would be an excellent opportunity to communicate with Affiliates, having previously begged for them to contact me to no avail.

There are two things that I would like to concentrate on in the Affiliate section of the next few issues as I feel that they are of utmost importance to young physiologists: retention of PhD-educated scientists and women in science. Has anyone else noticed the increasing popularity of medical/scientific writing as a career choice? In our department three PhD graduates/post-docs have left research for writing jobs over the past 3 months, and one is currently looking for such a post. Coincidentally, all are female. I asked them all why they no longer wished to work at the bench and the unanimous answer was that medical writing offered a permanent position and career opportunities that are hard to come by in academia or industry. The perception is that in industry, job security is non-existent, and in academia permanent positions are scarce. One academic said medical writers would probably spend an average of only 2 years in their job, making the length of the contract comparable to that of a post-doc anyway. Although this might be true, with a permanent contract the choice of whether to move on or not is the employee's, hence he/she retains control of future employment. This same academic also pointed out that by law, if an institution employs someone for 5 years on short-term contracts, it is subsequently obliged to offer them a permanent contract. I passed this comment on to a post-doc who has been at King's for 5 years on a contract that is nearing expiry. His reply was that he was not about to rock the boat by legally forcing his employer to take him on permanently. So, although this law is supposed to assist contract workers, it is unenforceable, as no one wishes to start their career with a reputation as a troublemaker.

Whilst browsing through the Higher Education Statistics Agency (HESA) web site, I picked out a couple of statistics that supported my perception of there being proportionally fewer women as one progresses up through levels of seniority. In the academic year 2003-2004 69% of anatomy, physiology and pathology students were female. At the undergraduate level 56% of students obtaining a first degree were female, but at the doctorate level this fell to 43% – unfortunately, the completion figures for science subjects alone are not available so these percentages are for all subjects. By the time we get to women academics, only 35% of full-time staff are female although, again, I have data only for all subjects. I am pretty sure that the proportions are even lower in science. Let's take our Society as an example: five of the 28 Council Members are female (18%). I don't think that this necessarily reflects inherent sexism within The Physiological Society, but rather that Council membership simply mirrors the fact that there are far fewer women at the senior level from which to select. Is female gender a barrier to a career in science or do the stats reflect a self-selecting academic population? A recent correspondence in *Nature* noted that both men and women rated women's research ability as inferior to that of similarly qualified men, when the gender is known (*Nature* **438**, 1 Dec 2005). Furthermore, female post-docs had to perform twice as well as males to achieve an equivalent peer-review score (*Nature* **387**, 22 May 1997).

In the next issue, one of my colleagues, Dola Akanmu, mother-of-two and currently PhD student-awaiting-viva examines if babies and benchwork are compatible. If you wish to contribute your views (you don't have to write a full article) email me at patricia.de_winter@kcl.ac.uk

Patricia de Winter
King's College London

Young Physiologists' Symposium

The first Young Physiologists' Symposium to incorporate a European Society for Free Radical Research (SFRR) 'Free Radical School' was held at Aston University and The Belfry on Friday, 8 July 2005

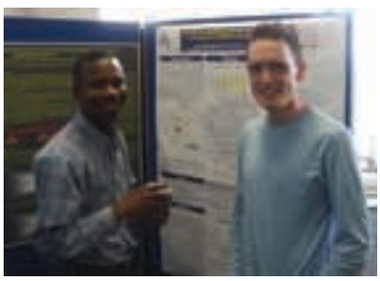
Young scientists from across the globe were given the opportunity to present their work and 18 oral and eight poster communications were presented by participants from several European countries, the USA and Japan.

Kelvin Davies (University of Southern California, 3rd from right) with YPS delegates following his talk at Aston University.

Considering that this YPS was held on the day after the tragic terrorist events in London, all participants should be congratulated on their perseverance in negotiating the ensuing transport chaos to arrive in good time!

As the meeting was held immediately before the 2005 annual SFRR meeting, the topics mainly covered physiological responses to oxidants and antioxidants, and ranged from the benefits of enriching human diets with vitamin C, soy or almonds to the modulation of gene expression, cell signalling and DNA damage. We were especially honoured that Kelvin Davies, Professor of Gerontology and Biological Sciences at the University of Southern California and outgoing President of the International SFRR, delivered the keynote lecture on oxidative stress-related diseases and ageing to close the YPS. All of the young physiologist's presentations were of an extremely high standard and it was only after much deliberation that an overall winner for the best YPS presentation could be finally selected. Milos Filipovic, (University of Belgrade, Serbia and Montenegro) won this award for his enthusiastic talk on nitric oxide and manganese superoxide dismutase. All participants appreciated the opportunity to share their research experiences during the poster sessions held over lunch and coffee breaks.

Following our successful symposium, YPS delegates joined the main SFRR meeting for an evening barbeque, reception and sessions over the weekend held at The Belfry near Birmingham. Apart from the unique opportunity to play golf at the home of the PGA and Ryder Cup, a novel aspect of this YPS was that it continued over the next 3 days as part of the Free Radical School 'breakfast club', held every morning at 8 a.m. before the main sessions! These early morning sessions allowed young scientists to have informal discussions with experts in the field, and were led by Angelo Azzi (University of Bern, Switzerland) who discussed his work on vitamin E, Jose Viña (University of Valencia, Spain) who examined free radicals in the ageing process and Giovanni Mann (King's College, University of London) who shared his views on cardiovascular diseases. Despite the early start, these sessions were very well attended and spawned lively discussions between the young scientists and the mentors, but time was limited and the main meeting always came too quickly.



Above: Some of the YPS delegates at the evening SFRR barbeque reception held at The Belfry. Right: PhD students Amos Fatukun (University of Glasgow), left, and David Rowlands (King's College London) at the YPS poster session.

The Physiological Society also sponsored a symposium at the SFRR meeting on *Lipid peroxidation, oxidative stress and cardiovascular disease* organised by Giovanni Mann and Enrique Cadenas (University of Southern California). In addition to the organisers, speakers in this well attended session included G Poli (University of Torino, Italy), P Thornalley (University of Essex), A Martinez-Ruiz (CINC, Spain), E Halligan (Leicester Royal Infirmary), L McLellan (University of Dundee), M David-Dufilho (CNRS, France), F Etienne (University of Louvain, France) and A Banning (German Institute of Human Nutrition).

Finally, we would like to thank everyone who made the YPS such a great success – all the organisers and generous sponsors, but especially the YPS delegates themselves for attending and presenting their work. It only remains for us to urge more societies to promote such dedicated symposia for young scientists alongside their main meetings and to encourage international networks of younger scientists.

Melissa Grant
Aston University, Birmingham, UK
Richard Siow
King's College London, UK
Co-organisers

National Science Week

Science knees up! Medical engineering of the joints

Dr Martin Knight will host a hands-on lecture at Queen Mary, University of London, Mile End Road on 13 March at 3 p.m. This stimulating lecture is targeted towards 6th form students, although anyone with an interest in medical engineering is welcome to attend. For further details please contact Irrum Magre (imagre@physoc.org) or visit http://www.physoc.org/education/

Related information

Nobel Laureate to give keynote lecture at King's College London in National Science Week (p.18)
Science learning with a difference (p. 52)

Medical education and the arts

There is increasing interest in the inclusion of the arts in the medical curriculum. It was recently reported that almost half the medical schools in the United States involve the arts in learning activities (Strickland *et al*. 2002). Use of the arts is said to serve a number of functions such as improvement of clinical skills, promotion of humanism and as a learning tool.

Medical students are often gifted musicians or artists and arts related-activities allow the students opportunities to express their creativity in a way they can seldom do during the undergraduate medical course.

At the School of Medicine, King's College London, I have developed two special study modules focusing on the links between medicine and the arts. The first, *Bodyworks: Images of the Body in Western Art*, has at its foundations the basic science discipline anatomy, and is for second year medical students. The course explores thematic imagery and concepts involved in the representation of the body in art and draws parallels with aspects of medical practice. It includes lectures, seminars, tutorials and visits to art galleries enabling students to explore the themes in the context of visual art theory and practice and to consider connections to the medical context. Dr Rosa Maria Letts, an art historian who lectures at the Victoria and Albert Museum, has given two informal presentations, one on Renaissance sculpture and one on the bodies at Pompeii.

Since this module proved to be very popular with the students, a second module was developed on music and medicine, focusing on psychology. We look at the origins of music, how music is perceived and processed by the brain and the physiological and psychological responses to music. This led on to consideration of psychotherapy and music therapy. Speakers include Dr Aaron Williamon (Royal College of Music), Ian Noonan (Nursing and Midwifery at St Thomas' Hospital) who speaks on madness in music with a live performance of some of the songs discussed, and Sarah Lenton (broadcaster and writer) who examines the representation of doctors and disease in opera. One student was so inspired that, although she had never been to the opera, she chose tuberculosis in music as the theme for her assessment, presenting the 'case notes' of Violetta (Verdi's *La Traviata*) and Mimi (Puccini's *La Boheme*). Overall the students produce imaginative high quality work with topics ranging from 'Sex, drugs and Schubert' to 'Musical Savants'.

The Tales of Hoffman (Royal Opera House) from Sarah Lenton's talk

(*photo by Clive Barda*)

A number of colleagues have expressed interest in putting on such a course, but are unable to find time to put the material together. I plan to make the courses available on CD/DVD and would be grateful if anyone who is interested or who has any ideas on the project would contact me.

Mary L Forsling
Department of Medicine, St Thomas' Hospital, London, UK.

Reference

Strickland MA, Gambala CT, Rodenhauser P (2002). Medical education and the arts: a survey of US medical schools. *Teach Learn Med* **14**, 264-267.

Celebrity diets, obesity and hormones: what does science have to say?

Donna Brown, The Society's Education Officer, and I ran a session at the British Association's Festival of Science in Dublin on 8 September 2005 aimed at young people. A lively discussion ensued with our speakers, after their presentations exploring various current myths about dieting, metabolism, exercise and managing weight control. The session was chaired by Stuart Warmington (Trinity College Dublin), and the line up of speakers included Claire MacEvilly (Medical Research Council), David Haslam (National Obesity Forum), Nicole Lowe (University of Central Lancashire) and Karen Birch (University of Leeds).

Thorny issues tackled included the dangers of the various extreme, and often celebrity promoted, diets including Atkins, nutritional myths promoted in the media, the extent of the rising tide of obesity in the UK and the diseases such as diabetes and cancer that are apparently linked to it, and the need to engage in physical activity to protect your health. The latter had a particularly strong message for women and girls – taking enough exercise is vital for healthy weight control approaches, however health and the female reproductive hormones are all strongly connected. Women and girls who over-diet or over-exercise to the extent that their menstrual cycles shut down can lose the protective effects of oestrogen and progesterone, with consequent health implications for maintaining a healthy heart and bones, and the risk of bringing on health problems normally only seen in menopausal women. The attendant media lapped all this up and we had good coverage of the event in the papers next day.

And what did a middle-aged lady like myself learn from this? Moderation is the key, i.e. don't eat more than you can burn off, take more exercise, but don't overdo it (not a big risk in my case!) and eat a nutritionally balanced diet to promote health without being obsessive about weight control.

Donna and I love doing these sort of events on behalf of The Society. Next year we are planning to attend the BA Festival in Norwich in September with an event for young people on Regenerative Medicine. If you would like to contribute, you are very welcome to contact Donna or myself at dbrown@physoc.org or ebell@physoc.org.

Liz Bell

The Physiological Society

Founded in 1876, The Physiological Society is a learned society with approximately 2,500 Members (including 14 Nobel Laureates) and Affiliates (younger scientists) drawn from over 50 countries. The majority of Members are engaged in research, in universities or industry, into how the body works or in teaching of physiology. The Society's main aims are to promote the advancement of physiology and to facilitate communication, both between scientists and with other interested groups. To achieve these objectives, The Society supports 4-5 scientific meetings annually, organises International Workshops, publishes two journals and awards grants to allow Members to travel to scientific meetings and to carry out research collaborations. Interaction with outside bodies is encouraged through representation on various councils and committees, and active membership of the Biosciences Federation and the Federation of European Physiological Societies.
http://www.physoc.org

Structure of The Society

As detailed is its governance documents, the activities of The Society are overseen by an Executive Committee of seven members and a Council of 28 members Much of the development and implementation of The Society's activities is devolved to a number of committees, each of which focus on a particular area of interest. The Society is supported by an Administrative Office in London and a Publications Office in Cambridge (with 10 employees in each office).
http://www.physoc.org/members/committees/
http://www.physoc.org/contacts/

Executive Committee

The Executive Committee comprises a President, Chairman and Vice-Chairman, Treasurer, International Secretary, Meetings Secretary and Editor-in-Chief of *The Journal of Physiology (ex officio)*.

Administrative Office (London)

The staff in the London Office comprise a Chief Executive Officer, Deputy Executive Secretary/Head of External Affairs, Personnel Officer/Accounts Administrator, Committee Secretary/Office Administrator, Accountant, Education Officer, Membership & Grants Officer, Meetings Administrator, Events & Membership Assistant and International Programme Administrator.

Publications Office (Cambridge)

The staff in the Cambridge Office comprise a Managing Editor, IT Manager (*The Journal* and The Society), three Production and Copy Editors (*The Journal of Physiology*), Senior Publications Administrator and two Publications Administrators (*The Journal of Physiology*), Executive Editor/Editorial Administrator (*Physiology News*/*The Journal of Physiology*) and a Publications Executive (*Experimental Physiology*).

Activities of The Society

Scientific Meetings and International activities

Activity at scientific meetings is driven largely by the Special Interests Groups (SIGs)), each of which is led by one or two SIG Convenors. The Society supports an Annual Main Meeting in July each year, four or five Focused Meetings, Special Symposia and Non-Society Symposia. Scientific meetings and symposia may be held jointly with other societies, in the UK or internationally. As part of its international activities The Society supports International Workshops that are aimed at physiologists at an early stage in their careers. The Society supports the scientific meetings of the Federation of European Physiological Societies (http://www.FEPS.org) and International Union of Physiological Sciences (http://www.IUPS.org). It hosted the annual FEPS meeting in Bristol in 2005 and will co-host it jointly with the Slovakian Society in 2007 in Bratislava and will host the scientific meeting of IUPS in 2013.
http://www.physoc.org/meetings
http://www.physoc.org/international

Publications

The Society produces a monthly electronic *Newsletter* for Members and a quarterly magazine *Physiology News*, which keeps Members and others informed about interesting science and Society news. The Society publishes two journals, *The Journal of Physiology* (http://jp.physoc.org) and *Experimental Physiology* (http://ep.physoc.org), and a series of Monographs. The abstracts of work presented at scientific meetings are published electronically as *The Proceedings of the Physiological Society.*
http://www.physoc.org/publications

Outreach activities

The Society supports workshops for teachers of physiology and participates in UCAS Education Conventions and BSF careers events. Publications of The Society include a number that aim to enthuse undergraduates and schoolchildren about physiology as a subject and to provide information about the use of animals in biomedical research. The Society also lobbies Government and other organisations on issues relevant to its Members and promotes awareness of physiology in the media.
http://www.physoc.org/education

Funding opportunities

Information about grants available, including the Departmental Seminar Scheme, Network Interaction, Non-Society Symposia, Vacation Studentships and International Centres of Excellence and Junior Fellowships can be found on The Society's web site. Grants are also available to Members and Affiliates to attend scientific meetings and to collaborate with other laboratories in the UK and abroad.
http://www.physoc.org/grants

How can I join?

Joining The Society is a straightforward and transparent process with clear guidelines. For further information go to:
http://www.physoc.org/join

How can I benefit?

As a Member you:

- are provided with information about The Society's activities via the web site, the *Newsletter* and *Physiology News*
- can have online access to The Society's journals
- can become a member of one or more of The Society's Special Interests Groups, which will enable you to participate more actively in the scientific meetings of The Society
- can apply to the various grant schemes.

How can I contribute?

As a Member

- organise Research Symposia at Main Meetings
- organise Focused Meetings, Special Symposia, and Non-Society Symposia
- nominate Prize and Public lecturers
- vote at AGMs and EGMs to help shape the workings of The Society, develop its policies and determine the membership of Council and Executive Committee.

As a SIG Convenor

- organise special interest sessions at Focused and Main Meetings
- coordinate the process of scrutineering of abstracts, in order to help maintain scientific excellence and integrity within your subject area
- meet annually with the Meetings Secretary and other members of the Meetings Committee to help formulate the strategic development of The Society's scientific meetings
- liaise with members of your SIG to develop scientific initiatives within your subject area.

As a Committee Member

- play an active role in implementing The Society's objectives within a given area of activity
- play an active part in developing strategy and shaping the budget within a given area of activity.

As a Council Member/Trustee

- play an active part in the strategic development of The Society's activities
- ensure good governance of The Society
- play a role in the selection of the Executive Committee and of Honorary Members.

The Physiological Society Meetings Calendar 2006

Meeting	*Place*	*Date*	*Type*	*Abstract submission opens*	*Abstract submission closes*	*On-line Programme available*	*Published as Proceedings of Physiological Society*	*Members' Grant Application Deadline*	*Affiliates' Grant Application Deadline*
German Physiological Society & FEPS	**Munich, Germany**	**26-29 Mar**	**FEPS**	**Nov 2005**	**12 Jan 2006**	**Jan 2006***	**No**	**31 Jan 06**	**31 Dec 05**
Frontiers in Epithelial Transport	Manchester	6-7 Apr	Focused	9 Jan	18 Jan	3 Mar	Yes	31 Jan	29 Feb
Basic Science of Cystic Fibrosis	**Algarve, Portugal**	**20 Apr**	**Focused**	**Dec 2005**	**24 Feb**	**Jan 2006****	**No**	31 Jan	29 Feb
Physoc Main Meeting	UCL	5-7 July	Main	13 Feb	13 Mar	1 June	Yes	31 Mar	30 Apr
Joint International Meeting with The Brazilian Physiological Society	**Ribeirão Preto, Brazil**	**27-30 Aug**	**Joint Intl**	**March**	**April**	**TBC**	**No**	**18 Feb 2006 Meeting specific scheme*****	**18 Feb 06 Meeting specific scheme*****
Control and Modification of Excitation-Contraction Coupling in Healthy and Diseased Muscle	Heidelberg, Germany	13 Sept	Focused	26 Jun	5 July	9 Aug	Yes	31 July	30 June
New Developments in Stress Physiology	**Bristol**	**4-5 Dec**	**Focused**	**28 Aug**	**6 Sept**	**4 Nov**	**No**	**30 Sept**	**31 Oct**

- * For further information please visit **http://physinst.web.med.uni-muenchen.de/dpg06/**
- ** For further information please visit **http://www.europeancfconference.org**
- *** A limited number of travel grants to attend the meeting in Brazil will be available. Up to 50 individuals may be supported. Applicants will be required to submit an abstract of the work they are intending to submit for the meeting and will be required to produce evidence of registration. For further information and a meeting specific application form please visit http://www.physoc.org/meetings/

Parliamentary and Scientific Committee

I attended two interesting meetings of the Parliamentary and Scientific Committee this Autumn – one on complementary medicine with Giovanni Mann, Chairman of The Society's Executive Committee, and one on African science and technology development with our new International Programme Administrator Laura Pinson. The Society is a member of the Committee, established in 1939 as a primary focus for liaison on scientific and technological issues between Parliamentarians and scientific bodies, science-based industry and the academic world. The main aim is to focus on those issues where science and politics meet, informing Members of both Houses of Parliament by indicating the relevance of scientific and technological developments to matters of public interest and to the development of policy. The Committee meets once a month, when Parliament is sitting, to debate a scientific or technological topic and its relationship with political issues.

Complementary and alternative medicine (CAM): should it be provided on the NHS? took place on 17 October. The speakers were The Lord Walton of Detchant (Chairman of the Inquiry into CAM by a sub-committee of the House of Lords S&T committee), Professor Stephen Holgate (MRC Clinical Professor of Immunopharmacology, University of Southampton) and David Tredinnick MP (Joint Chairman, All-Party Parliamentary Group for Integrated and Complementary Healthcare). The debate looked at the issue of the increasing number of GPs who recommend CAM therapies to their patients (40% recommending and some 20% offering CAM services at their surgeries).

Lord Walton emphasized that his Inquiry had taken a long hard look at the various CAMs on offer and considered evidence of efficacy. Osteopathy and chiropracty had been found to be reasonably well institutionalized and seemed to offer proven benefits to patients, so Bills regulating these had already been passed through Parliament. Other CAMs that showed self regulatory cohesion, provided training and had some evidence that they were useful included herbalism, acupuncture and homeopathy. Lord Walton defined these as his category 1 therapies. Category 2 therapies, such as reflexology, seemed to have some evidence of usefulness in complementing main stream medical treatments. Category 3 therapies, including ayurvedic and ancient Chinese medicine needed a great deal of further investigation, as although well established in their communities, their founding paradigms were not well understood. There had also been some concerns about known harmful ingredients such as heavy metal poisons in some Chinese medicines. We suggested that the Committee might approach the Chinese mainstream medical establishment to see if they had made any headway in analysing their own traditional medicines. Lord Walton also had an 'unclassified' category for those CAMs where there seemed to be little or no evidence of any efficacy, such as crystal therapy

Lord Walton summed up by saying that the Inquiry had concluded that the social role of the therapist and placebo effects could explain some of the benefits obtained by CAMs, it was well known that busy GPs could often not give their patients the same levels of quality time as CAM practitioners, but not all of the observed therapeutic benefits could be explained away by this. The important policy question for Government now was whether any CAMs should be funded through the NHS and, with limited budgets, what should be given priority. He considered that introducing some therapies into the NHS might lead to some cost savings. For example the herb St John's Wort is known to be useful in treating depression and can be cheaper than prescribing some main stream drugs, and osteopathy and chiropracty could make inroads into the treatment of chronic back problems. He thought that the next step should be to encourage each CAM area to rigorously self regulate, develop core curriculums in their training to include anatomy and physiology, and that clinical trials should be conducted. The UK also needed centres of excellence in our universities looking at CAMs. The findings of the Inquiry had been debated by the Lords in 2001and subsequently accepted by Government.

Professor Holgate reported his interest in clinical trials and the complexities of human health. The debate between conventional medicine and CAMs had often been unhelpfully polarised and it was important to try to move beyond this and find the common ground. Conventional medicine was struggling in some areas, notably the management of chronic disease, with patients' increasingly stressful lifestyles leading them to feel fragmented and disempowered, and increasingly concerned about the perceived possible side effects of mainstream drugs. Health services now need to address the question of an integrated approach to health, looking at diet and lifestyle issues, and going beyond treating illness to promoting the improvement of health and well being in the population. Humans are very complex animals, with health being a holistic self regulated state where the whole is more than the sum of its parts. Conventional medicine may have taken too disaggregated an approach, attempting to focus on the individual components of disease. In contrast to this, the intelligent body hypothesis views the body and the brain as a self organising, self regulating system. The placebo effect may well prove to be an important therapeutic principle in treating the whole system and research is beginning to highlight this. Brain imaging has demonstrated that placebos can mimic active drugs and activate the same brain areas. His conclusion was that the NHS needs to move to integrate a spectrum of approaches to the management of complex disease, and that it was in this area that CAMs and conventional medicine might effectively interact.

David Tredinnick emphasized that he is well known as an enthusiastic advocate for CAMs, to the extent that he has even been called the MP for health food

retailers Holland and Barrett. He had noted that in the past CAM practitioners had been relatively isolated, even from each other. He had brought practitioners together from the various areas to debate their involvement in health provision. The general public also seem to be voting with their feet with a sharp rise in their use of CAMs. CAM remedies are now on sale in high street chemists. He considered that CAM should be used to plug effectiveness gaps in conventional medicine, such as in the treatment of back pain, stress, and nausea.

After much lively debate, the meeting concluded with a general feeling that some CAM therapies should be offered on the NHS to plug existing weaknesses in provision. However, this might best be done by offering a small number of the well regulated ones first, notably chiropracty and osteopathy. Others might then be added to the NHS menu at a later date when they are considered appropriate.

The importance of science, engineering and technology to a sustainable economy on the African continent took place on 12 December. The speakers were Sir Crispin Tickell (Former Ambassador to the UN), Professor Frank Rijsberman (Director General of the International Water Management Institute), Professor Richard Carter (Institute of Water and Environment, Cranfield University) and Professor Sir Gordon Conway (Chief Scientific Advisor to the Department for International Development (DFID)). All of these presentations emphasised the Government's current drive to help Africa develop in the science and technology area to tackle its manifold economic, environmental, educational and health problems. The presentations specifically focused on issues of water development which were not particularly newsworthy in physiological terms. However, all speakers did emphasise that western aid to Africa needed to build on home grown expertise and talent, rather than attempting to unthinkingly apply foreign solutions to African problems. This gave us the opportunity to say that the new aid initiatives being developed should liaise closely with the UK learned societies, as most societies had African members who could help with grassroots initiatives. Laura and I will be following this up with DFID and the Royal Society for Chemistry.

If any Members have an interest in helping us to develop new programmes in Africa, please contact us.

Liz Bell

Competing with football in Dublin

John Bryant (immediate past-president of the Society for Experimental Biology, pictured above) represented the Biosciences Federation recently when he spoke at their Café Scientifique event which was held during the British Association for the Advancement of Science's Festival of Science in Dublin in early September.

Bravely contending with the Ireland vs France World Cup qualifying match which was being shown in the bar below (and from which we could hear every cheer and groan), John gave a brilliant performance with his talk entitled *Science promise vs science reality*. When the promised data projector and screen failed to materialise,[1] John had to abandon his PowerPoint illustrations and change the emphasis of his talk to engage his audience with a good deal more discussion than they had been expecting. Taking as his initial example the topic of embryonic stem cells that had been highlighted by the BA's President, Robert Winston, he compared the actual current state of the art with scientists' statements about the promise of stem cell technology. He went on to analyse in more depth the whole topic of *Science and the spin*, illustrating this with several comparisons of the way that mid-20th century and early 21st century discoveries were presented.

With the welcome arrival of refreshments (which included, according to Chris Willmott of Leicester University, the best spicy chicken wings he had tasted since his time as a post-grad in New York[2]), John handed the initiative to the audience who were encouraged to work in groups to discuss the possible reasons that scientists in the 21st century are much more likely to make bold public claims about the applications of their work than earlier generations. This was followed by a general discussion as the groups presented their views. We all agreed that in an age where sound-bytes and hype are increasingly the norm, scientists faced with such headlines as *Gene discovery brings hope for millions* or *GM crops can feed the world* have a responsibility to help the wider public understand the difference between science fact and science fiction. Overall, despite the problems, the audience seemed to enjoy the evening, as did the local organisers of Dublin's Alchemists' Café, who hosted the event.

Education and Public Affairs, Society for Experimental Biology

Deceased Honorary Member

The Society reports, with regret, the death of A David M Greenfield. David was elected as a Member in 1944 and an Honorary Member in 1987. A tribute will be carried in the next issue of *Physiology News*.

[1] A clear example of the difference between promise and reality!

[2] Did this, John wondered, give a whole new dimension to the term 'winging it', an activity that had been forced on him that evening by the lack of a data projector. Was the talk spicy enough to qualify for a similar accolade?

A word from the Education Officer...

I now have 8 months experience working as the Education Officer for The Physiological Society and I think I can finally say that I have found my feet! Not being one to tiptoe around, within my first month I agreed to brave a number of sixth form events, present to postgraduates, mingle with teachers, and spent a considerable amount of time networking.

The year 2005, from an Education perspective, was very successful. The Physiological Society was represented at a number of schools' events, UCAS conventions, and workshops for teachers and sixth formers (see reports on opposite and on p. 52). We ran a 'sell-out' session at the BA Festival of Science in Dublin (see report on p. 50) which was subsequently featured in a number of newspapers. During the later part of the year, in collaboration with The Biochemical Society, The Institute of Biology, The Society for General Microbiology, The British Pharmacological Society, The Institute of Horticulture, and supported by The Biosciences Federation, we ran a biosciences careers conference and gave over 500 graduate/postgraduate students and postdocs the opportunity to hear about, and tips on pursuing, a variety of careers.

I am hoping that 2006 will be just as eventful. We are already putting together a session for the BA Festival of Science (as detailed in Celebrity diets, obesity and hormones) and we are sponsoring an event at King's College, London, during the BA National Science Week (see Nobel Laureate to give keynote lecture at King's College London during National Science Week on p. 18). The bioscience careers conferences will be held on 4 and 18 November and 2 December. For further details see the BSF website from September (http://www.bsf.ac.uk/careers.htm). We have tentative dates for sixth form and teachers' workshops; however, there are still grants available to run additional workshops – if you have a physiology-based activity appropriate for sixth formers or secondary school teachers (one they can take back into their classroom), and you are interested in running a workshop please contact me (dbrown@physoc.org).

If you would like to get involved with any of our educational activities, or have ideas of your own or an interest in helping to redevelop our education web pages, I would love to hear from you.

Donna Brown

Teachers' Workshop at Coventry University

Physiology is fun was the approach for a recent teachers' workshop hosted at Coventry University. The idea behind the event was to offer a refresher course for biology teachers in some laboratory techniques and to provide ideas for biology A-level practical classes. The event was organised in collaboration with Society Education Officer Donna Brown and Melanie Hanna from Bio-Rad Laboratories Ltd.

After a welcome cup of coffee the teachers were straight into the lab, and they had all remembered to bring their labcoats, unlike the students. Melanie ran the practical sessions superbly well with the able help of Palak Heywood. Initially, Melanie produced a variety of fish and the teachers may have been forgiven for thinking it was *Ready, Steady, Cook*.

The idea behind the first practical on protein finger-printing was to extract the proteins from fish muscle and run an electrophoresis gel to separate the proteins. Melanie had provided a comprehensive booklet on the lab sessions and gave clear introductory talks on the underlying theory. The teachers got to work on mashing up the tissue, boiling, extracting and running the gels. The Bio-Rad electrophoresis equipment was affordable and easy to set up for school labs and the teachers proved adept at loading the gels.

After a coffee break, while the gels ran, the gels were stained with coomassie blue to show the protein bands. All the gels produced a nice array of bands, which the teachers were justifiably proud of, with particularly prominent bands for actin and myosin. There were clearly visible differences between the protein bands for the different species of fish, which Melanie cleverly linked back to evolution. I couldn't help thinking that the remains of the fish samples would have made a nice bouillabaisse!

We then moved on to a nice demonstration of size exclusion chromatography, using a coloured solution and simple, cheap columns. The two coloured components were visibly separated by the column and fractions were collected. In doing this, the teachers had an insight into research: 5% inspiration, 95% perspiration!

After lunch (fish was definitely off the menu) we moved on to an entertaining introduction to ELISA. This involved role play as travelling sales representatives exchanging bodily fluids! Each person selected a tube of solution and went round the lab merrily mixing their fluid with that in other people's tubes, to an accompaniment of disco music! We all then ran a simple and quick ELISA, using the fluids in our tubes as samples. Some of the samples were found to be positive in the ELISA and some were negative. The protein is question was supposed to be from an infective agent. By

Getting to grips with protein finger-printing

analysing the number of positive and negative results it was possible to illustrate epidemiology in action and identify the two original culprits, one of whom was the initial 'Typhoid Mary'.

The day was rounded off nicely with a tutored wine tasting by our resident wine expert, Steve Smith (I can personally recommend the wine courses at Coventry University). Very positive feedback on the day was provided by the teachers, with comments like: challenging, exciting, stimulating, relevant, an excellent day really well delivered, excellent in terms of quality and the hands-on opportunities, highly enjoyable. Some of the teachers asked for a similar future event, but based on exercise physiology.

Ray Carson
Physiology and Sport Science, University of Coventry, UK

Science learning with a difference

With only 24 places on offer for this 1 day interactive sixth form workshop, I was overwhelmed by 150 requests for places. The workshop was organised and run by Martin Knight a researcher and lecturer at Queen Mary University of London, and held at Tower Hamlets City Learning Centre in December 2005. Designed for sixth form students with an interest in medicine, biology, physiology or medical engineering, the workshop focused on joints such as the knee and hip, examining joint injuries associated with trauma or disease, and the clinical repair techniques including tissue engineering.

Martin Knight started the workshop with a short lecture describing the anatomy of the knee, function of the cartilage and the necessity for exercise. The initially shy sixth-formers were eventually coaxed out of their shells when Girish Pattappa (PhD student/demonstrator performed a hoof joint dissection and asked them all to put on gloves and feel the cartilage. Despite the protest of 'yucks' and 'you must be joking' even the most squeamish of students had a quick touch. With the dissection over Martin

.Girish Pattappa performs a hoof joint dissection.

started the next part of his lecture with a picture of a rugby player having his knee bent backwards during a match (not one for the faint hearted), and this led nicely onto knee arthroscopy and keyhole surgery used to examine, and in some cases treat, joint injury. A 'used' knee replacement implant was passed around the group whilst we heard about how this surgery was performed. Martin then described chondrocyte (cartilage cells) transplantation and revolutionary cartilage tissue engineering.

With a dramatic change of topic Reza Ben Gajra (animation support) gave the group an introduction into animation, a subject which the students were particularly knowledgeable about and even knew that it took the creators of Wallace and Gromit 5 years to make at 18 shots/second, 5 seconds a day! The idea was to use animation to explain the science they had learnt during the

Martin Knight helps students create their animation.

earlier lecture. With heads full of facts, and desperate to start moulding plasticine, the students were split into groups with the objective of developing a short animation to describe one of the following elements of the lecture: the structure of the knee, articular cartilage, cartilage injury and diagnosis, total joint replacement, chondrocyte transplantation and future tissue engineering treatments.

The students started off by drawing a story board to explain their given topic. The idea was to be as creative as possible, and as creativity rose so did the noise levels! Quotes such as 'This is going to be fun man' and 'Arrrr that's wicked' clearly showed how much fun they were having. And amongst the fun and laughter the students were learning; their coming-together animations clearly showed that they understood the science.

Not wanting to spoil the show (the animation will eventually be posted on our website) I thought I would just mention a few highlights: a physco-style knee replacement operation, a giant smiley knee after a bouncing chordrocyte transplantation and a visit to the 'bioreactor spa' and 'detox clinic' for cartilage tissue generation – the future ... With the animation complete the students recorded the voice-over and the final film was left in the capable hands of Adele Goodwin (City Learning Centre) to edit. The day was a huge success; all those involved thoroughly enjoyed themselves and, more importantly, the students went away having learnt about the knee and current, and indeed future, treatments of knee joint injury.

Due to popular demand Martin also ran an interactive lecture attended by approximately 50 students from schools surrounding Queen Mary University of London. After the lecture the students were given the chance to chat to Martin and some of his colleagues, and fuelled by drinks and snacks this part of the session was also well received.

We are hoping to run a similar event during 2006. Do please contact me for more information (dbrown@physoc.org).

Donna Brown

BIOSCIENCES FEDERATION

Student employability – whose job is it?

Colloquium organisers (from left to right): Dariel Burdass, Sarah Blackford, Sue Assinder, Jane Taylor, Donna Brown, Olga Zolle and Hannah Baker

This was the title of the Biosciences Federation's second Education Colloquium in October 2005, where professionals from the education, careers and employment sectors came together to discuss employability issues and to answer this topical question. The bulk of the delegates were academics and careers advisers from higher education, but there was also representation from school teachers and educational and policy professionals. Disappointingly, the industry sector was represented by only two delegates, one from English Nature, the other from AstraZeneca, but the presence of recruiting firms and organisations such as the Bioindustry Association and bioKneX allowed us to share an overall wide variety of viewpoints for the discussion sessions.

But what exactly is 'employability'? What do employers want, and how should employability skills be provided? During her introduction, Sue Assinder (Colloquium Chair) noted the various descriptors that have entered the everyday language of the teaching world: core skills, toolkit, graduate qualities, key skills, tertiary literacies, springboard competencies. She left the audience with the questions 'How are these skills being provided?' and 'Is it working?'

The morning was split into three sections (Schools, Higher Education and Employers), each containing two talks.

Schools

Kath Skillern (Edexcel) explained Edexcel's new GSCE science curriculum, which was developed to make science accessible to all students. It enables students to experience the science that affects them in their everyday lives in a relevant and interesting manner using either a content or context-orientated approach. The specifications are based on the QCA criteria. The students have to evaluate evidence, consider the implications of science on society and demonstrate knowledge of how science is practiced including explaining, theorising and modelling. The framework is flexible and students are able to choose from GCSE Science, GCSE Additional Science and also separate GCSEs in Biology, Chemistry and Physics. Those that choose to study GCSE Science alone will not be able to study science at A-level. In addition, 360Science also includes the BTEC First Certificate and Diploma, which allows students to study for a vocational qualification.

In terms of employability, concerns were raised by the audience that maths is still not embedded into the science curriculum and field work is not mandatory as it is for geography. The multiple-choice examination system remains, which some in the audience believed would compound the increasing problems of poor literacy and essay-writing skills.

Anna Cleaves (Anglia Ruskin University) reported on some extensive research which she carried out on the formation of science choices in secondary school (*International Journal of Science Education* **27** 471-486). Her work was driven by the drop in uptake of science in schools and the increasing tendency for biology to be taken with a range of other subject combinations. Students were surveyed longitudinally at the beginning and end of year 9, the end of year 10 and directly after they had made their choices in the spring of year 11.

Anna divided the student's choice into various 'trajectories':

- *Directed trajectory* where students have a long-term desire for a career in science. They tend to be inspired by highly visible professions such as sports science.
- *Partially resolved*: these students are still experimenting between science and the arts.
- *Funnelling* where a student is slowly gaining interest in science over time due to the topics and the quality of teaching (this group was poorly represented).
- *Multiple projection*: these students are very indecisive about their career choices and favour different careers at different times.
- *Precipitating trajectory*: these students are generally good at most things so they are spoilt for choice and find it difficult to decide which subjects to take.

One alarming fact that emerged from the survey was that, even amongst high achieving students with A grades for GCSE science, there was an overall image that science is too hard and that they are not clever enough to study it to A-level.

Anna finished her talk with a number of suggested ways forward: keep improving science teaching, provide bursaries for 'real science teachers', utilise careers advisers who know about science careers, and encourage exploration about science careers.

Higher education

'What is a bioscientist?' was the opening gambit for Jane Taylor's (Lancaster University) talk. She suggested that there are three types of bioscience student: those who want to become a practising scientist, those wishing to apply their knowledge to a bioscience-related industry and those who enjoy biology but do not want to use the knowledge directly in their

future employment. This creates a dilemma for the average academic who is left wondering how to meet everyone's needs, and specifically how to balance specific knowledge and generic transferable skills in their course material. In addition, many students are now coming to university with insufficient knowledge of maths and chemistry, an assessment-driven motivation and low level literacy skills. All of these are problems that are having to be redressed by academics during the degree course.

The other major issue for academics is student awareness of what transferable skills are and why they need them. In an assessment-driven culture many students will not be motivated to undertake these parts of the course unless they are embedded. Even if this is the case, students invariably are unable to identify which transferable skills they do have. In addition, Jane pointed out other short-comings of new students who arrive at the university with their heads stuffed full of information but with little understanding or the ability to express their own ideas and thoughts either verbally or in writing.

Jane concluded by saying that a long-term and concerted effort is currently needed to overcome some of these dilemmas, including reducing the amount of assessment and testing in schools, fostering critical thinking, and a better communication between schools and universities.

Ian Hughes (HE Academy Centre for Bioscience) reported on a survey which he conducted recently and which is published in the Centre for Bioscience's online journal, *BEE-J*, at www.bioscience.heacademy.ac.uk/journal/vol6/beej-6-2.htm. The conclusions of his findings from a longitudinal study of students who had graduated 1-2 years previously showed that graduates felt they had been well prepared by their university course with respect to theory and knowledge, presentations and communications skills, basic IT needs, confidence, organisation and time/self-management. However, they felt they were ill-prepared for practical aspects of their jobs, career management, specialist knowledge, advanced IT and commercial awareness.

Quotes such as '*You come out of uni expecting to walk into a job but in actual fact all graduates have the same experience and so the realisation that you need more at an early stage would be good*' will probably make most course providers and careers advisers throw their hands up in exasperation as they strive to introduce students to the Careers Service as they arrive at university. Similarly, another quote '*The hardest part was customer contact, day after day, question after question*', illustrates that students come out of university unable to make the connection between part-time temporary and full-time employment.

Ian's final take-home message was 'There are easy ways in which we can improve employability aspects of our courses. Use the existing tools and don't re-invent the wheel.'

Employers

Kay Wardle, managing director of science recruitment company RSA Consulting, was able to give the employer's perspective setting out the wide variety of jobs available within the bioscience industry. These include research, clinical trials, toxicology, regulatory affairs, sales and marketing. The three main requirements employers look for are a good degree in a relevant subject, practical work experience and transferable skills (see below). Her concluding remarks led on very well to the next talk as she told the audience that a good degree is not enough.

Our concluding talk of the morning from Andrew Whitmore (Careers Centre, University of Manchester) began with some professional definitions of the word 'employability', the most poignant of which was a quote from Peter Hawkins: 'To be employed is to be at risk, to be employable is to be stable'. Competition for graduate jobs is tough, illustrated by information which says that from a pool of 160,000 graduates entering employment in 2005, only 18,000 will enter formal 'graduate training programmes', leaving 142,000 entering junior roles within a wide range of employers.

Andrew divided the skills and qualities most in demand into five main categories:

- self-reliance skills (self-promotion, self-awareness, networking)
- people skills (teamworking, communication, leadership)
- general skills (problem-solving, entrepreneurial, numeracy, commitment)
- specialist skills (specific occupational skills, technical skills)
- commercial awareness.

Whilst a good percentage of bioscience graduates enter occupations directly or indirectly related to their degree, statistics show that over 70% do not. This emphasises the need for general employability skills in the curriculum.

Discussion

Following these formal talks, the delegates came back together for the discussion session, ably and efficiently managed by Sue Assinder. Sitting at round tables, the delegates were given three of the following questions to discuss and then feedback informally:

- how can we improve communication between stakeholders?
- are transferable skills really transferable?
- how can students take responsibility for their own employability skills?
- what could employers do?
- is there a 'core' knowledge base for a bioscience graduate? If so, what is it?
- how do you give students experience of the workplace?
- how can we break the mould of assessment-driven learning?

The results of the discussion and feedback are not reported here but a formal document will be published early in 2006. This will make recommendations that complement the findings and recommendations of the Biosciences Federation's *Enthusing the next generation* group which was published in November. We welcome any input and comments from our members about their views and experiences on student employability.

Sarah Blackford, Dariel Burdass, Sue Assinder
Education Committee, Biosciences Federation

The PowerPoint slides for all the talks can be viewed at www.bsf.ac.uk/edu.

The neurobiology of pain

Molecular and cellular neurobiology
Edited by Stephen Hunt and Martin Koltzenburg
2005 Oxford University Press. 403 pp, £60.00
ISBN 0-19-851561-8

This is an interesting collection of 15 invited papers dealing with the molecular and cellular aspects of the neurobiology of pain, but very little data on central processing of data in the brain is included, perhaps reflecting this field of research. There is, however, an interesting chapter on central imaging of pain (Flor and Bushnell) towards the end of the book and good chapters on organization of periaqueductal grey matter, including integration of pain behaviours (Lovick and Bandler) and descending control of pain processing by Gebhart and Proudfoot . The book is not divided into sections, making relationships between chapters more opaque than necessary.

The first two chapters are good overviews of the molecular biology (Caterina *et al*.) and plasticity (McMahon and Priestly) of nociceptors. Two chapters are devoted to studies of the dorsal horn giving details of its molecular architecture (Todd and Ribeiro da Silva) and mechanisms of modulation and central sensitization (Salter and Woolf). Mechanisms of neuropathic pain and its relentless persistence are then considered by Koltzenburg, who concludes that peripheral and central mechanisms for the generation and maintenance of neuropathic pain remain largely unexplored. A chapter on targets in pain and analgesia (Dickenson and Suzuki) follows and is succeeded by chapters on ascending pain pathways (Hunt and Bester), spinal delivery of drugs in pain control (Yaksh and Mantyh) and an excellent chapter on the development of pain systems by Fitzgerald and MacDermott. This is followed by a good review of visceral and deep somatic pain (Laird and Schaible). The final two chapters are on headache (Goadsby and Ferrari) and control of cancer pain (Mantyh and Yaksh).

Production is quite good, but four colour plates are placed in the centre of the book, all but one of them dissociated from their text. Perhaps more use of colour throughout the book would have resolved this problem. There are the usual weaknesses of edited books, but the chapters are interestingly written by people deeply involved in the subject.

Bill Winlow

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Zuckerman: scientist extraordinary

By Bernard Donovan
BioScientifica Ltd, Bristol.
506 pp, £24.95
ISBN 1-901978 24 9

One day in May 1966, shortly after the general election, I was sitting on the top deck of a London bus travelling down Oxford Street towards my laboratory in Drury Lane. Having narrowly failed to get elected to the House of Commons as a supporter of Harold Wilson's 'white heat of scientific and technological revolution', I was thinking about science and politics, and the new Government the PM was forming, when a news-bill caught my eye. 'Atom wizard called to Number 10', it said. Intrigued, I leapt off the bus at the next stop and bought a copy of the *Evening Standard*, to find that the wizard in question was Sir Solly Zuckerman, then the Government's Chief Scientific Adviser.

Lord Zuckerman OM, FRS, as he became, was an early exemplar of those bright young South Africans who left their homeland for postgraduate work in Europe or America, never to return. Sydney Brenner, Bennie Kaminer and Lewis Wolpert are more recent members of the same group. Born in 1904, Zuckerman arrived in London in 1925 with first class honours, and a Masters degree in Anatomy, to do the clinical part of his medical training (which could not then be done in South Africa). Hardly an 'atom' wizard – I think the sub-editor had confused him with Sir William Penney, another Government Adviser – but wizard he certainly was.

In the 1920s and 30s young Zuckerman made his way in scientific circles in London and Oxford. In the manner of the times he also met many luminaries in science, politics, literature and the arts, making contacts and friendships useful to him later on. Like many young scientists he disagreed with some of his mentors, in this case about the anthropology of human and ape skulls that he had begun to study in

South Africa. These controversies helped make his scientific reputation, and a substantial section of the book is concerned with both the arguments and the long-term outcome of the work. He also worked on human and ape endocrinology, particularly of the reproductive cycle, studies that foreshadowed the later discovery of the contraceptive pill. The endocrine field was then still in its infancy, and Zuckerman fostered it by founding and editing a major journal (*The Journal of Endocrinology*). At the outbreak of World War Two he was appointed Professor of Anatomy in the University of Birmingham.

When the war came, and in the aftermath of the Fascist bombing of Guernica, there was much concern about probable bombing casualties. I once heard J D Bernal, another major British scientific figure and one of my personal heroes, tell the story as follows:

'*Solly Zuckerman knew all about monkeys, so we staked out some on Salisbury Plain at various distances from a 500lb bomb and detonated it. Then we tried to extrapolate the effects on humans.*'

Practical science, no doubt, and surely necessary at the time, though one shudders to think of the reaction of today's animal protection lobby.

Bernal and Zuckerman went on to carry out (for the Ministry of Home Security) a seminal study of the economic and morale effects of air raids on Birmingham, showing that long-anticipated disaster and panic should not occur with the attack levels then possible. I can testify personally to the accuracy of their conclusions, having spent the war years in London through both Blitz and V-weapons. We Londoners were certainly scared, cowering nightly under staircases or in cellars while bombs fell and guns raged, but in the mornings most of us came out alive and got on with our normal lives.

Zuckerman subsequently joined Combined Operations, becoming an adviser on bombing policy. He had clear ideas on the optimum way to use offensive air power, considering that, with the limited bombing accuracy then possible, empirical evidence demonstrated that attacks should be concentrated on rail marshalling yards and engine repair facilities so as to paralyse the enemy's transport system. These opinions, developed in the Sicilian campaign, often disagreed with military wisdom, particularly with that of the United States Air Force in the run up to the D-Day landings. Zuckerman's views seem largely to have been vindicated when enemy records later became available.

This comprehensive biography by Bernard Donovan, covering all aspects of Zuckerman's professional and public life, is well-written and well-researched and should surely be of interest to many members of The Physiological Society. It is organised in blocks covering the different aspects, so that it is occasionally difficult to detect the chronological life of the man. In a book of more than 500 pages, with copious references and quotations, there are inevitably parts that will be of more or less interest to an individual reader, but this does not detract from the worth of the book. From my personal perspective I was fascinated by the wartime accounts, and the post-war political experiences.

After the war Zuckerman continued as Chief Scientific Adviser under successive Conservative and Labour Governments, first to the Ministry of Defence and later to the whole Government, on a three-days-per-week basis. His academic life in Birmingham meanwhile continued in the remainder of his time. In the 1960s he resisted Harold Wilson's attempts to bring him directly into the political process as a Minister in the House of Lords. Remembering the lack of political impact of those who succumbed to such blandishments, including Patrick Blackett, Alun Gwynne-Jones and CP Snow, this was probably a very wise decision. As a consequence, Zuckerman survived in Whitehall until formal retirement and remained as a part-time adviser, with a room in the Cabinet Office, into his eighties. Only in the Thatcher years did his influence wane, largely because the Prime Minister considered herself to be her own science adviser.

The index of this book is a roll-call of the science and defence questions that came before post-war Governments; Skybolt, TSR2, 'independent' nuclear weapons, Thor missile deployment, Hawker-Hunter VTOL aircraft, the Thames Barrier and so on. Many of these were costly failures, but some were outstanding successes. Zuckerman's advice was sought on all of these, but in the culture of amateur Ministers was not always taken in full. There were few, if any, empirical (biological) scientists in the Commons during the period; after my failed attempt in 1966 it was more than 30 years before Dr Ian Gibson was elected in 1997, though sadly he has never been given Ministerial rank.

It is appropriate to end a review of this excellent book by remembering two particular achievements of Zuckerman the man. Among all his other activities he achieved the reform of the Zoological Society in a Promethian struggle against long-established privilege, involving two cases in the High Courts. Sadly, though, despite his advice the London Zoo remains one of the few national zoos in Europe not to have Government funding. Perhaps his crowning moment, though, was his reaction to the Cecil King-Hugh Cudlipp coup-conspiracy in 1968; I am delighted that it was a scientist who declared 'this is rank treachery', which it certainly was (pp 500-501). It is no exaggeration to call Solly Zuckerman 'scientist extraordinary', and this book does justice to his multiple roles, and many achievements.

Gerald Elliott
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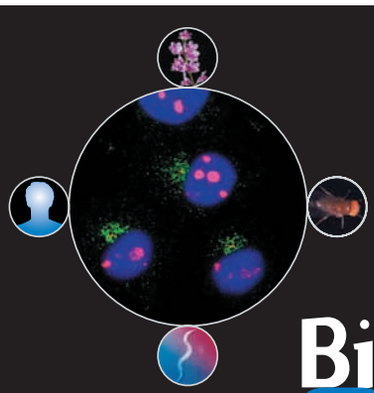

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