# PHYSIOLOGYNEWS

spring 2004 | number 54


Featuring:

Glasgow meeting
Images of Manchester & Cambridge

Whither physiology departments?

Making an Olympic champion
What's new in anaesthesia?
Saving British science
Twenty years of Society magazines
A career for the retired physiologist

A publication of the Physiological Society

# Cambridge Meeting

More images from the Cambridge Meeting appear on p. 7
*(Photos by Prem Kumar)*

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

Published quarterly by the Physiological Society


### Contributions and Queries

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

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





ISSN 1476-7996



The Physiological Society is registered in England as a company limited by guarantee, No 323575. Registered office: PO Box 11319, London WC1V 6YB. Registered Charity No 211585.

Printed by The Lavenham Press Ltd

### Cover photo

The Department of Physiology at the University of Birmingham (see Editorial and Letters)

# PHYSIOLOGYNEWS

## Contents

## Action Points

### Grants

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

### Membership applications

Applications are received throughout the year and have no deadlines.

### Change of address

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

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

## Forthcoming scientific meetings

Newcastle (22-23 July 2004)

Cork (1–3 September 2004)

Oxford (1-3 October 2004)

London (18-20 December 2004)

Joint meeting with the Chilean Physiological Society

Seville, Spain (10-13 February 2005)

Sponsored symposia in association with the Spanish and Dutch Physiological Societies

Bristol (20–23 July 2005)

### Abstract submissions

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

## *Physiology News*

Letters and articles and all other contributions for inclusion in the Summer 2004 issue, No. 55, should reach the Publications Office (lrimmer@physoc.org) by 12 April, 2004. Late copy can be included if space permits.

## Suggestions for articles

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

## *Physiology News* Online

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

## 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 dénouement or conclusion.

### Length of articles

This will be determined by the subject matter and agreed between the contributor and the commissioning editor. Articles will vary in length from 500 to 2,000 words.

### Submission of articles

Authors should submit text in the form of a disk or emailed Word document, to reduce the risk of introduction of errors during re-typing.

### Submission deadlines

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

### Illustrations and authors' photographs

Authors are encouraged to submit diagrams, drawings, photographs or other artwork to illustrate their articles or, if they cannot provide these themselves, to suggest appropriate illustrations. A photograph of the author(s) should also accompany submissions.Photographs may be colour or black and white, prints or transparencies or TIFF files **with a minimum resolution of 300 dpi**. Electronic colour figures should be saved in **CMYK mode**.

### References

Authors are requested to keep the number of references to a minimum – preferably no more than two or three. Please cite all references in the style of *The Journal of Physiology* (see *Instructions to Authors 2004*, http://www.physoc.org).

## (Some) changes at *Physiology News*

This issue of *Physiology News* is a significant one for me personally, as it marks my moving across from the Deputy Editor's chair to take over as Editor from Bill Winlow. This will not be heralding any radical change in the style or look of the magazine – we are proud of *Physiology News* and I see our main task for the next few years as maintaining the high standards that have been set during Bill's reign.

Which is not to say we are complacent. We do hope to introduce a couple of new regular features in the next issue or two – details next time. And as we have reiterated in these pages, the magazine serves, and reflects, the Physiological Society and its Members. If you have suggestions for the magazine, or feel you could do better, then please write to us and tell us how.

Finally, I also want to say a formal 'Thank You' to Bill for his work over the last five years. *Physiology News* as it now is owes a lot to his stewardship. In particular, the highly successful revamp in 2002 was Bill's baby, reflecting a lot of time and effort put in by him and by the Executive Editor(s), initially Sheila Greaves and latterly Linda Rimmer. It has been a pleasure to work with Bill, and I am very pleased that he will be staying on the editorial group for the foreseeable future – when he can spare time from his exhausting new schedule in the medical writing fast-lane - see below!

# Whither physiology departments?

As 2004 dawns, the tide of renamings, rebadgings, restructurings and amalgamations of physiology groupings in UK universities continues, fuelled by the usual mix of institutional strategy - I use the term loosely - and RAE preparation (or fall-out).

Even such a bastion as the Physiological Laboratory in Cambridge is now likely to be merged with Anatomy in the near future. As most UK-based Members will know, in the last RAE fewer than a dozen departmental groupings were actually submitted under the physiology Unit of Assessment.

It thus seems pretty clear that most Physiological Society Members in UK academia now ply their trade under different departmental banners, typically in larger multi-disciplinary 'super-departments'.

Our President, Alan North, referred in his brief speech at the AGM in Manchester to the need to promote our discipline specifically in this context of the decline of stand-alone physiology departments.

While we can hopefully all take individual steps to promote physiology, what sort of new structures would university physiologists like to be a part of? How big a department do we want to work in? Who do we want as colleagues? These are questions where our collective response –at least at an institutional level – might have some weight.

Based on numerous conversations over the last five years or so, I have the impression that physiologists are fairly content being amalgamated with pharmacology departments, perhaps unsurprisingly given the shared interests (and perhaps even shared society memberships). Marriages with cell biology and biochemistry seem rather less happy, perhaps because many of us fear power imbalances in such conglomerates between the big-money (cell biology and biochemistry) and not so big-money (physiology and pharmacology) scientific strands. In general, however, those who have become part of larger units have usually survived better than they perhaps expected. Discipline identity does not die, provided existing communities of labs with similar interests are recognised, maintained, and encouraged.

There can also be advantages in amalgamation, although this may make some Members wince. The most obvious gains have been in enhanced RAE scores for a number of the keenest amalgamators. Some may detect a self-fulfilling prophecy in this. However, RAE gradings inarguably mean real money, and more money allows the other 'three Rs' - recruitment, retention and refurbishment.

The worst-case scenario, in contrast, is almost certainly the atomization of a department, and the partitioning of its personnel piecemeal into several other, perhaps geographically distant, parts of a University. Olga Hudlicka's letter in this issue (p. 40) paints a vivid picture of how this can completely destroy a department, leaving the future of the discipline in the institution in doubt. It is this scenario that we need to fight to avoid.

But why, some university managers – and even maybe some professors of physiology – will argue? Such dismantling of a department is usually argued to be a way to respond to changing priorities – to create a trans-disciplinary centre in one or more areas, for instance, by bringing together researchers from different disciplines. The loss of an old department, in this view, is merely moving with the times, playing to the institution's strengths and abandoning structures that no longer make sense.

So who is right? The answer depends, perhaps, on what one views as most important – the institutional imperatives, particularly in research, the need for a clear institutional 'home' for the discipline, or – last but by no means least – the needs of the people who work in the institution. Of course, all of these are linked, not separate. In particular, in these days of regular re-structurings it bears restating that the success of institutional initiatives does not depend just on whether a new plan – for instance for a multi-discipline centre – is a good one.

It also depends, critically, on the people who make up the centre – or any other new structure - being able to work together effectively. Indeed, one of the arguments for amalgamation – rather than atomisation - is that it can preserve useful discipline groups, but can also prevent their 'sclerosis' by fostering useful new interactions.

Which brings me to a truism: departmental communities, and the research collaborations they foster, are fragile entities that take time to grow (organically?) and are easily disrupted. Although scientific collaborations do not depend absolutely on old-style shared tearooms and libraries, these kinds of places, where people meet and talk in informal settings, are clearly important in enabling researchers to recognise the like-minded.

It is in this context that atomizing departments makes no sense. How long does it take to re-establish fruitful scientific interactions and collaborative links in new departments, with new neighbours?

Sadly, these more ephemeral research interactions are not easy to measure. But that doesn't mean they are not important. How do we quantify the 'added value'conferred by a tearoom, or a sense of belonging? I do not know. But I would like to think that professors, deans and institutional planners are considering these very questions as they plot the next phase of reorganisation.

Austin Elliott

# Welcome to Scotland

Physiologists at Glasgow, Strathclyde and Caledonian Universities look forward to welcoming the Society back to the north in March, writes Godfrey Smith


Top: North view from the West Medical Building illustrating the classic Victorian architecture prevalent in Glasgow. This is Park Terrace, with Kelvingrove Park below

Above: The new Glasgow Science Centre and Glasgow Tower viewed from the top of the Gilbert Scott Building, Glasgow University

Right (top): The River Kelvin flows past the West Medical Building, Wolfson Building and Davidson Building complex

Right (bottom): The weathercock on top of the clock tower of the Gilbert Scott Building indicates the date (1887) of the 'new campus' of Glasgow University on completion of the movement of the campus from the town centre to the healthier airs of the west end of Glasgow

*(Photographs by David Miller)*

Glasgow University colleagues have been active in the Physiological Society since its inception, and the history of the department continues to mirror the worldwide development of biomedical science. The Institute of Physic (subsequently Institute of Physiology) was created in the mid 19th century. The Regius Chair of the Theory of Physic was established in 1839 and its 2nd incumbent, John Gray McKendrick was one of the 19 present at the meeting in 1876 which set up the Physiological Society, proposing the rules of membership and those governing the Society's officers. Biochemistry and Pharmacology seceded from physiology in the mid 20th century before they all came together again in 1994, along with the rest of Biology, as the present incarnation - the Institute of Biomedical & Life Sciences (IBLS).

The University currently has 10 professors who either have 'physiology' in their titles or are active Society members. Most are in IBLS's Division of Neuroscience and Biomedical Systems. IBLS is organised in a matrix system with separate management of teaching and research. It has approximately 180 full-time academic staff in six research divisions, a graduate school, and an undergraduate school which organises teaching and learning.

The previous Physiology Department is now a part of the Division of Neuroscience & Biomedical Systems (N&BS) located mainly in the West Medical Building, and the adjoining, recently constructed, Wolfson Building. The Division currently has 37 academic staff, ~40 post-docs and ~70 postgraduates. Historically the Division was well founded on integrative biology at the cellular, organ and organismal levels and it is steadily incorporating the molecular level. When the biochemists left in the 1960s they took the precaution of leaving a 20






From the top: Ian McGrath (regius Professor of Physiology and Head of the Division of Neuroscience and Biomedical Systems within the Faculty of Biomedical and Life Sciences ); Billy Martin (Professor of Cardiovascular Pharmacology); Ann Ward (Technician; Godfrey Smith (Professor of Cardiovascular Physiology); John McCarron (Reader in Physiology); and Jim Morrison (Advisor of Studies in Physiology)
*(Photographs by Francis Burton)*

metre gap before starting their new building. The current generation decided to bridge the gap in recognition of the integrated direction of biomedical science and the Wolfson Foundation and MRC were good enough to back our arguments with hard cash. This has had an excellent scientific impact. The integrated nature of IBLS and the new physical proximity have lead to useful cross-fertilisation. An unexpected benefit has been the Wolfson Courtyard, which has become a popular events venue.

N&BS operates three main research themes - cardiovascular science, neuroscience (Spinal Cord Group; Neuropharmacology) and exercise science and medicine, which follow the 'thematic research priorities' of the University. We play a leading role in university-wide schools of cardiovascular studies, neuroscience and respiratory science. This has been extremely effective in facilitating collaborative programmes with clinical departments and between IBLS's divisions.

Each of the thematic groups has successfully created major initiatives – e.g. the Cardiovascular Group (Martin, McCarron, McGrath, MacLean, Miller, Smith) who use a series of cell physiology and pharmacological techniques to study both cardiac and smooth muscle.

In Neuroscience we have established a Spinal Cord Research Group bringing together strengths in neuroanatomy and neurophysiology (Maxwell, Riddell, Todd & Cobb). The Division is also home to the Yoshitomi Research Institute for Neuroscience in Glasgow (YRING), a collaboration with the Japanese Pharmaceutical Company (Morris, Stone and Harvey & Pratt from Strathclyde University). The recent appointment of Brian Robertson to the chair of Neuroscience at Strathclyde and Trevor Bushell's appointment as the Glaxo-Jack Lecturer are welcome additions to the group of physiologists within the city.

The Centre for Exercise Science and Medicine (CESAME) brings together strengths in this field across the University, with an emphasis on exercise for health. This aims to use our strong biomedical research environment to bring cell and molecular science into whole body applied physiology (MacFarlane, Pitsiladis and the recently appointed Jason Gill).

N&BS has particular strength in biological imaging, ranging from cardiac and vascular tissue (Smith, McCarron, McGrath) to the CNS (Maxwell and Todd). The addition of molecular biology and transgenics, through links within IBLS and strong links with Physiology, Pharmacology and Biophotonics at Strathclyde, is creating a strong cross-thematic imaging centre.

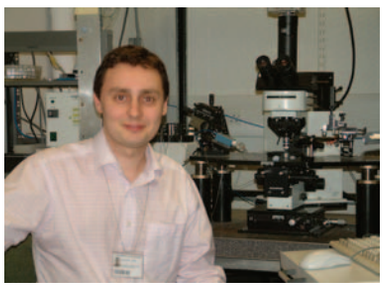
The undergraduate school serves over 2,000 undergraduates from science, medicine, veterinary medicine and dentistry. Virtually all of these students are taught (or learn) physiology in their 1st and 2nd years, mostly in integrated courses, which recognise no disciplines. This seems to work since we earned 'Excellent' in all teaching assessments: cell and molecular biology, organismal biology and medicine.

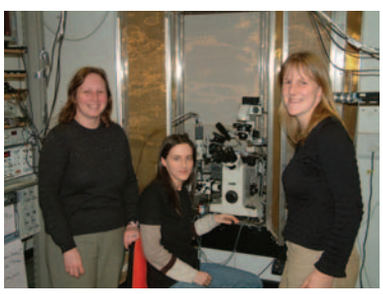
The recently opened Wolfson Medical Building is the first purpose-built centre for medical education at Glasgow. The building is a striking addition to the campus and has won a recent Scottish Design Award. The medical curriculum is 'student centred' with most learning in clinically based exercises from the first year on rather than having pre-clinical followed by clinical years. At its core is an integrated programme of clinical and scientific work, which is pervaded by physiology, and 'special study modules' – designed to allow study in depth – which have a strong physiological content. Theoretically this should mean less systematic physiology in years 1 and 2 but more physiological science in years 3 to 5. Certainly the amount of teaching by physiologists has not declined!

The ability of the Institute to provide integrated courses for Science (BSc) students from year 1 has resulted in far more students throughout the biomedical and Life Sciences learning

some basic physiology. The majority of our 900ish BSc cohort take physiology modules in year 2, while in the Honours years (3 and 4) units and modules containing physiology are taken by around 300 students. In terms of specialisation, Honours in Physiology are taken by around 20 and Honours in Physiology & Sports Science by ~100.

The city of Glasgow also contains major groupings of physiologists at both Strathclyde and Caledonian Universities. All three campuses are within a 20 minute underground train trip of each other and the academics in these departments are increasingly linked by collaborative grants and research projects. Glasgow physiologists look forward to welcoming the Society back to our fair City. For more information visit our Divisional web site at: www.neuroscience.co.uk.





Top (left): Stuart Cobb (Lecturer in Neuroscience)
Top (right): David Miller (head of IBLS graduate school)
Above (left): Andy Toff and Rosie Spike (part of the Spinal Cord Research Group lead by Andrew Todd, David Maxwell and John Riddell)
Above (right) Members of John McCarron's research group - left to right: Karen Bradley, Debie MacMillan and Susan Chalmers
*(Photographs by Francis Burton)*

# It's not all deep fried you know...

## Some fine places to eat and drink around Glasgow

I moved from London to Glasgow a little over a year ago, and yet I am still surprised and impressed by the huge number of places to wine (or drink 'heavy') and dine in this fabulous city. Perhaps I don't get out much. But you should try to avoid at least some of the deep vein thrombosis induced by sitting in the lecture theatres at the Society Meeting in one of Glasgow's 'other' universities, and sample some of our fine places to eat and drink. This is a subjective list of places to try, but I've consulted some of my younger, trendier colleagues and some of the natives for suggestions.

Glasgow University is in the centre of the West End, which is a target-rich environment with excellent bars and restaurants within easy reach. Recommendations for more traditional bars on Byres Road are **The Aragon** and **Tennents** - the latter does great pub grub at low prices. Classier places are **Booly Mardy's** (Vinicombe St, just off Byres Road; yes, an intentional wordplay on my favourite tomato soup), which is cool for cocktails, and in Ashton Lane, the new **Loft Bar & Restaurant** is packing folk in with good food, music, and drinks.

Also well worth a visit in Ashton Lane are **The Ubiquitous Chip**, which has two atmospheric bars, as well as an excellent, though pricey, restaurant (look out for the recently restored Alasdair Gray murals on the walls). This tiny lane also boasts a Belgian beer bar, **Brel**, which, I'm reliably informed, does substantial plates of mussels between 5 and 7 pm. While in that area, why not visit the Hunterian Museum with the reconstructed Mackintosh house. Another pub for those who think we dress and live like Monarch of the Glen up here would be **Uisge Beatha** on Woodlands Road - there's a not too shabby selection of malts (127. I phoned) in the main bar. En route to Uisge Beatha is **Stravaigin**, on Gibson Street, which does wonderful, adventurous, food, but also has a regular and well stocked bar area.

For good restaurants in the West End, it's advisable to book ahead, but we like **Stravaigin 2**, **Café Andaluz** (a super Tapas bar in Cresswell Lane), **Two Fat Ladies** at 88 Dumbarton Road (superb fish, and cosy too).

But my very favourite eating place, amongst all I've tried in Glasgow thus far, is **No Sixteen** on Byres Road. In our own lab taste test it beat Gordon Ramsey's famed 'Amaryllis' and Nick Nairn's eponymous, and now departed, restaurant. (And it is much cheaper too. But don't try to get in on 31 March, as T*he Journal of Physiology* invades for their 'tea').

However, you should get out of the West End at least once - there's loads of places to try in town too, especially within walking distance of my own Uni. In the Merchant City, pop into **Rab Ha's** (Hutcheson St, named after a famous Glesca glutton); it boasts real character, real beers, and a fine restaurant below. Try the **Corinthian** on Ingram Street, simply to marvel at the architecture, though they've spoiled it recently with a more modern bar. Take the opportunity to pop into the adjacent Glasgow Museum of Modern Art. The **Blackfriars** (Bell St) is highly thought of for its real ales and homely atmosphere. Nearby, **Café Gandolfi** justifiably has a good reputation for imaginative food and now has a trendy loft extension with a bar that does light food up to 8pm. I'd also recommend you try **The Rogano** cocktail bar (11 Exchange Place). The cocktails are sublime, and both the beer and bar food are first-rate; it's pricey, but beautiful, and a grand place to impress someone (do not, under any circumstances, blanch when they bring your card back, and don't be a meanie, tip the cloakroom attendant). Nearby, in Mitchell Lane, is **The Lighthouse**, a significant venue for architecture and design exhibitions, with a very good cafe, and its associated **Bar Soba** - terrific Asian food. Opposite is **Bar 10** - with 'metro-European cafe bar vibe'.

One last Glasgow institution demands and deserves to be mentioned - **The Horse Shoe Bar**. It stands in a little alley near Central Station, and is an unreconstructed Victorian gem of a pub. For that special treat, it offers the best-value three course lunch I've ever come across, which has, incredibly, just broken the three pound mark. Try the homemade soup, with a pint of heavy. You won't want to go back for the afternoon sessions. A treasure of a pub.

As I mentioned, there are simply loads of places, and there are excellent guides available (e.g. **The List**) that will tell you everything you need to know about eating and drinking in Glasgow. Or ask someone who lives here. Some of our hosts in Glesca Yooni will produce a list. I hope you have a grand time, but don't blame me for giving a wrong steer…

My own favourite bar up here? Fill my bar up with raucous physiologists? Nae chance.

Brian Robertson
*Physiology and Pharmacology, University of Strathclyde*

## Making the news

The Physiological Society is, under normal circumstances, used to breaking new ground. But at this year's Cambridge meeting they undertook something truly experimental. In a break from tradition, the Society decided to promote the research on display and so, for the first time, a Press Officer joined the scientists mingling amongst the biscuit trays and industry stalls. Kindling interest was easy, as much of the work associated with the Society affects everyday people's lives and interests. Hence it wasn't a surprise when the initial press releases, sent out a week before the conference began, received considerable interest from the media. In every case, the researchers cooperated enthusiastically with the Press Officer's strange questions and requests for further information, even when it involved posing for television cameras or undertaking telephone interviews with Spanish reporters.

Paul Chantler, from Liverpool John Moores, underwent perhaps the greatest shock to the system, agreeing to be

Ben Wilson, the Society's freelance Press Officer at the Cambridge Meeting (top) and Paul Chantler, interviewed for British Satellite News (above)

interviewed for *British Satellite News* - an organization providing features and news to over 400 international television networks - on his study into the effects of ageing on heart output.

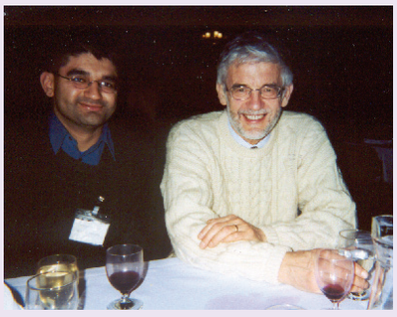
But Paul's was by no means a singular success. Avijat Datta, from the Medical Research Council's Cognitive and Brain Sciences Unit, not only underwent a telephone interview with the *New York Times* over his research into the brain wave warning signs of human mistakes, but was also interviewed live on air by an American radio station. All incidents were coped with admirably, even when *BBC News O*nline unfortunately decided to change his gender, a mistake thankfully now rectified.
(http://news.bbc.co.uk/1/hi/health/3330601.stm)

Paul Greenhaff's work, carried out at the University of Nottingham, was another study receiving international, as well as local, media interest. Details of his study, looking into the effects of creatine on glycogen storage, appeared in the food industry magazine *Nutra Ingredients*, amongst others.
(http://www.nutraingredients.com/news/news-NG.asp?id=48705).

The studies mentioned above are only a small selection of the coverage the Meeting received. Work has also appeared in some truly diverse places; from *Essex Radio* and DTI publications to *BBC Online* and the *New York Times*. Hopefully the success of this year marks the start of many more forays into the world of media by the Physiological Society and its Members.

Ben Wilson

## Images of Cambridge



Above: Neoclassical Downing College
Right: Corne Kros (front) and Society accountant Casey Early
Below (left): Gary Bhumbra with Richard Dyball
Below (right): Roger Thomas 'makes a statement' during the Society Dinner at King's College

Top: David Eisner, new International Secretary, marks Ann Silver's 40 years as a Member of the Society with a bouquet (see also p. 35 for other long-serving Members). Above: Sir Andrew Huxley (centre) with Dafydd Walters, Executive Committee Chairman (right) (*Pictures by Austin Elliott and Prem Kumar)*

# Physiological determinants of success in track athletics

In the first of a series of articles on exercise physiology, Andrew Jones considers what makes an Olympic champion as athletes prepare to compete in the Athens Games

Andrew Jones

The track athletics events (100 m, 200 m, 400 m, 800 m, 1,500 m, 3,000 m steeplechase, 5,000 m and 10,000 m), along with the marathon, will undoubtedly be among the 'showpieces' at the forthcoming Olympic Games in Athens. The male and female winners of these rather disparate events are rightly acknowledged as possessing extraordinary physical capabilities, which result from a combination of both genetic and training-related factors. The purpose of this short article is to briefly review the physiology of elite level performance in track athletics or, in other words, to consider the physiological factors which predispose Olympic athletes to be 'citius'(from the Olympic motto 'citius, altius, fortius' - faster, higher, stronger) than their non-athletic counterparts.

The limitations to athletic performance and the main causes of fatigue are closely linked to the principal metabolic pathways by which adenosine triphosphate (ATP) is re-synthesised to meet the energy demand of the exercise. At the onset of a race, the ATP stored within the contracting muscles is broken down to release energy to fuel muscle contraction. The average running speed that can be sustained in a race, and therefore the average rate of ATP turnover, is typically highest in the 100 m and falls as the race distance increases. For example, in the 100 m race (which has a duration of < 10 s in elite male sprinters), the average energy expenditure is ~ 4 $kJ.s^{-1}$ whereas in the marathon (which has a duration of ~ 2 h and 5 min in elite male runners), the average energy expenditure is ~ 1.7 $kJ.s^{-1}$. Obviously, therefore, it is important that ATP is re-synthesised at a very high rate to enable the attainment of the maximal running speeds required in sprint events, and for ATP to be re-synthesised at a moderately high rate but for long periods of time to enable the maintenance of the high (but sub-maximal) running speeds in long distance events.

The human body has a number of metabolic pathways which are well suited to meeting the demands of both high-intensity short-duration exercise and low-intensity long-duration exercise. What distinguishes an Olympic athlete from his or her sedentary counterpart is the athlete's extraordinary ability to liberate energy at a rapid rate from the appropriate metabolic pathway(s) and to limit and tolerate the development of fatigue as the race progresses. In the 100 m race, phosphocreatine (PCr) hydrolysis is the principal mechanism by which ATP is re-synthesised. This energy pathway can produce ATP at a very high rate, though only for a short period of time and, as such, it is ideally suited to meet the energy demand of sprinting. The maximal rate at which ATP can be broken down at the myosin ATPase to support muscle contraction and the rate at which ATP can be re-synthesised through PCr hydrolysis (and other metabolic pathways) are therefore the principal determinants of success in sprint events. It is therefore not surprising that elite sprinters generally possess an extremely high proportion (and a large number) of 'fast-twitch' fibres (which have a high activity of myosin ATPase and a high maximum power output compared to 'slow-twitch' fibres) in their locomotory muscles (Costill *et al.* 1976).

During maximal-intensity exercise, the finite intra-muscular stores of PCr can only support ATP re-synthesis for a few seconds so that other metabolic pathways become progressively more important as sources of ATP as the race distance increases. For example, during 200 m and 400 m sprinting, the $O_2$-independent breakdown of muscle


The physiological characteristics and capabilities of the elite athlete derive from a combination of genetic predisposition and arduous physical training

glycogen is responsible for the majority of the ATP re-synthesised. The high rates of muscle glycogenolysis in these events, however, results in a significant increase in lactic acid production. The consequent reduction in muscle pH has been suggested to be a cause of muscle fatigue in some circumstances (but see Westerblad *et al.* 2002). 'Anaerobic glycolysis' also makes an important contribution to ATP re-synthesis in the middle distance running events and the accumulation of lactate (and the fall in pH) is a possible cause of fatigue in these events too. In the 'long sprints' (200 m, 400 m and also, arguably, 800 m), therefore, the capacity to re-synthesise ATP at a rapid rate through 'substrate-level phosphorylation' and to tolerate the consequent disturbances to homeostasis are likely to be important determinants of performance.

Anaerobic glycolysis can produce ATP at a high rate, but it is unable to sustain this rate for sufficiently long to be the principal energy supply pathway for events beyond the 400 m. Rather, the energy supplied in middle distance and long distance running events derives principally from oxidative phosphorylation. At the onset of exercise, muscle oxygen consumption increases immediately but, in the elite endurance athlete, it takes approximately 1-2 minutes before the oxygen uptake ($VO_2$) approaches the 'steady-state' requirement for the running speed being maintained. This means that some athletic events are over before oxidative metabolism can make an appreciable contribution to energy supply. It should also be noted that, in the middle distance running events, the ATP turnover rate required will exceed the maximal ATP turnover rate that can be supported by oxidative metabolism. Nevertheless, the maximal rate at which an athlete can re-synthesise ATP through oxidative pathways (denoted by his or her '$VO_2$ max') is probably the most important determinant of performance in events from 800 m to 5,000 m (and possibly 10,000 m). This is consistent with the fact that the $VO_2$ max values of elite endurance athletes (70-90 $mlO_2.kg^{-1}.min^{-1}$) are typically twice those of age-matched sedentary people.

The relationship between an athlete's physiological capacities and likelihood of athletic success is not straightforward

The 10,000 m track race and the marathon are run at intensities below the $VO_2$ max (i.e. typically at 80-95 % $VO_2$ max) and other 'sub-maximal' physiological factors therefore become progressively more important in these events (Jones & Doust, 2001). One of these factors is 'running economy', which represents the steady-state oxygen cost of running a given distance (km) per unit body mass (kg). The energy cost of running at the same speed varies considerably between individuals but it is generally lower (i.e. running economy is better) in athletes. Possessing good running economy is important in long distance races because it means that any absolute $VO_2$, and therefore fraction of the $VO_2$ max, that is sustained equates to a higher running speed. The running speed above which muscle lactate production exceeds lactate clearance also correlates strongly with long distance running performance. Furthermore, the concept of 'critical velocity', which is given by the asymptote of the hyperbolic velocity vs. time to fatigue relationship, is useful in modelling performance potential in athletes (Fukuba & Whipp, 1999).

Finally, the ability to utilise fat as substrate for oxidative metabolism is important in sparing the oxidation of the limited endogenous carbohydrate stores. The depletion of muscle glycogen has been linked to the fatigue process, particularly in the marathon (Karlsson & Saltin, 1971). Again, in light of the preceding discussion, it is interesting to note here that endurance athletes generally have a high proportion of 'slow-twitch' muscle fibres in their locomotory muscles. Slow-twitch fibres generally have greater mitochondrial and capillary density, a greater capacity for fat metabolism, and may be more efficient at low forces relative to 'fast-twitch' fibres (Bottinelli & Reggiani, 2000).

It should be re-emphasised here that the energy pathways discussed above do not operate in isolation; rather, they are all activated at the onset of exercise. However, the relative contribution of the various energy pathways to the total ATP turnover rate will vary with the intensity and duration of exercise (which are themselves co-dependent). One important determinant of performance (at least for events > 400 m), which has perhaps been overlooked previously, is the rapidity with which oxidative phosphorylation can be 'switched on' at the start of a race. The rise in $VO_2$ following the onset of exercise is generally much faster in athletes compared to their sedentary counterparts, but this factor may even partially discriminate performance differences between athletes. In the transition from a standing start to, say, 1,500 m race pace, faster '$VO_2$ kinetics' will reduce the depletion of PCr and the accumulation of lactate and hydrogen ions, and reduce fatigue. Furthermore, the energy from substrate-level phosphorylation that is 'spared' as a consequence of the fast $VO_2$ response might be used subsequently in a sprint finish.

This article has highlighted the physiological factors (principal energy pathways and possible causes of fatigue) that contribute to the determination of performance in the athletic track events. The physiological characteristics and capabilities of the Olympic athlete derive from a combination of genetic predisposition and arduous physical training. While it is the author's belief that these physiological factors represent some of the most important determinants of

athletic success, it should be acknowledged that biomechanical, psychological, tactical, nutritional and environmental factors also have the potential to impact upon performance to a greater or lesser extent. Knowledge of the physiological demands and limitations to performance enables the exercise physiologist to assist in the construction of appropriate training programmes for athletes specialising in different events and to advise athletes on other (legal) performance enhancing strategies. These strategies include supplementation with creatine to increase the PCr content of muscle (for sprinters), with bicarbonate to increase buffering capacity (for middle distance runners), or with carbohydrate to increase muscle glycogen storage (for long distance runners). With the forthcoming Olympic Games taking place in the heat of Athens, appropriate strategies for acclimatisation and hydration are also very important (this is the topic of the next article in this series). There are clearly a large number of both physiological and non-physiological factors that can determine the outcome of a race such that the relationship between an athlete's physiological capacities and their likelihood of success is not straightforward. While this can be a little frustrating for the physiologist it is, of course, good news for spectators, broadcasters, and bookmakers.

Andrew M Jones
*Reader in Applied Physiology*
*Manchester Metropolitan University*
*Alsager, UK and Consultant Exercise Physiologist to UK Athletics*

References

Bottinelli R, Reggiani C (2000). Human skeletal muscle fibres: molecular and functional diversity. *Progress in Biophysics and Molecular Biology* 73, 195-262

Costill DL, Daniels J, Evans W, Fink W, Krahenbuhl G, Saltin (1976). Skeletal muscle enzymes and fiber composition in male and female track athletes. *J Appl Physiol* 40, 149-154.

Fukuba Y, Whipp BJ (1999). A metabolic limit on the ability to make up for lost time in endurance events. *J Appl Physiol* 87, 853-861.

Jones AM, Doust JH (2001). Limitations to submaximal exercise performance. In Eston R & Reilly T. Kinanthropometry and Exercise Physiology Laboratory Manual, Vol 2: Exercise Physiology.. Routledge, London.

Karlsson J, Saltin B (1971). Diet, muscle glycogen and endurance performance. *J Appl Physiol* 31, 203-206.

Westerblad H. Allen DG, Lannergren J (2002). Muscle fatigue: lactic acid or inorganic phosphate the major cause? *News Physiol Sci* 17, 17-21.

***In the next issue Ron Maughan writes on competing in the heat: hydration and thermoregulation as limiting factors***

## Images of Manchester


The Society's Joint Meeting with the British Pharmacological Society took place in the Stopford Building, University of Manchester from 9–12 September, 2003.

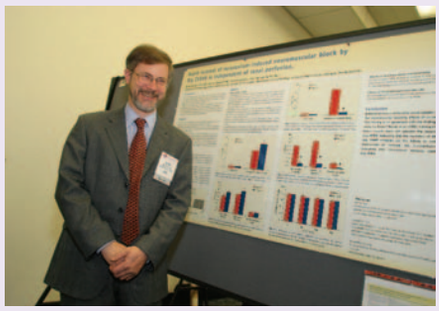
Local host, Arthur Weston, is pictured seated (left, top) with Meetings Secretary Bridget Lumb and Rod Flower aiding and abetting behind.

Left, centre: Camera-shy Meeting co-organiser, Daniela Riccardi (right) with Cathy McCrohan and other guests (left, bottom) enjoyed the reception kindly hosted by Blackwell Publishing at the Whitworth Art Gallery to mark their launch of *The Journal of Physiology* and *Experimental Physiology* from January, 2004.

Delegates enjoyed the Society Dinner (far left) which took place at the Yang Sing Cantonese restaurant. Karl Kunzelmann (Regensburg), guest lecturer in the epithelial transport and renal session is pictured with Cathy Garner (Huddersfield) (far left, top) and BPS President Rod Flower delivers his speech at the Dinner (far left, bottom).

# What's new in anaesthesia?

Bill Winlow describes some of the safety aspects of anaesthesia, including a new compound that reverses neuromuscular blockage, closed loop feedback systems for monitoring anaesthesia and current ideas on brain protection in neurosurgery



Top: Bill Winlow consults James Cottrell, the outgoing President of ASA, after his lecture on brain protection in neurosurgery *(Photo: Jay Kelly)*
Centre: Ton Bom with his poster on the Organon reversal agent at the ASA meeting *(Photo: Jay Kelly)*
Above: The new Glasgow conference centre (the Armadillo) overshadowed by an original dockyard crane *(Photo: David Murray)*

In my new role as a medical writer, I edit a newsletter entitled *aspects* in *anesthesia* on behalf of Organon Inc, and this entails a good deal of travel to report on meetings. Between 31 May and 3 June I attended Euroanaesthesia 2003 In Glasgow. This was an historic joint meeting of four European societies and was hosted by the Association of Anaesthetists of Great Britain and Ireland. There was a very comprehensive programme of refresher courses, together with presentations and discussions of the latest research, primarily in Europe. Later in the year, 11-15 October, I went on to the American Society of Anesthesiologists (ASA) annual meeting in San Francisco. This was an enormous meeting with over 17,000 participants. There were review lectures and refresher courses to suit all tastes as well as a wide range of posters and a very large trade display. Here are a few of the presentations from these conferences that interested me, particularly in terms of patient safety.

## Postoperative residual curarization – a continuing problem

For general anaesthesia three main groups of drugs are given: hypnotics to induce unconsciousness, analgesics to reduce pain during and after surgery and muscle relaxants to produce complete muscle paralysis during surgery. Neuromuscular blocking agents (NMBAs) are therefore, an essential adjunct to patient care during anaesthesia (see box 1).

Jørgen Viby-Mogensen, Denmark, presented data showing that myths about postoperative residual curarization (PORC) – such as it has no clinical significance or that it can easily be avoided by using clinical tests, or an intermediate-acting muscle relaxant for intubation, etc. – are not true. Although there are numerous relatively reliable tests to detect PORC, such as 5 sec sustained head lift, leg lift, hand grip, etc. he said that these alone would not always identify it. Furthermore, it would appear that such tests are not used routinely. According to a recent Danish survey of 251 anaesthetists, >50% could not distinguish between reliable and unreliable tests and <50% used reliable tests on a daily basis. In addition, 75% did not know that clinically significant PORC could not be excluded by tactile or visual evaluation of response to nerve stimulation. There is no suggestion that anaethetists elsewhere are any better at distinguishing PORC than their Danish counterparts!

Professor Viby-Mogensen presented data showing that clinically significant

### Box 1 The use of neuromuscular blocking agents in anaesthesia

The use of neuromuscular blocking agents (NMBAs) is of great importance in anaesthesia, where they are used to paralyze the patient, thereby allowing endotracheal intubation and surgery at light depth of anaesthesia, without patient movements. This procedure allows the more rapid recovery of patients following anaesthesia, but patients may be left with prolonged paralysis after termination of the NMBA, extending the period before recovery of independent respiration and extubation. Thus an ideal NMBA should be rapid in onset, short-acting and rapidly reversible.

#### Types of NMBAs

Two types of NMBAs are available, both of which bind to postsynaptic nicotinic receptors at motor end-plates.
**Non-depolarizing agents** compete with acetylcholine (ACh) in binding to unoccupied end-plate receptors. They are split into two further structural categories the aminosteroids (e.g. rocuronium, vecuronium and pancuronium), and the benzyl isoquinolones (e.g. mivacurium, atracurium and cis-atracurium.
**Depolarizing agents** cause persistent depolarization of the postsynaptic membrane to prevent muscle action potentials, by locking Ach receptor channels open to allow sodium influx for prolonged periods. Only succinylcholine (suxamethonium) is now in widespread use. It increases blood pressure, may increase or decrease heart rate and causes high levels of histamine release, but it has the shortest onset duration (60-90sec) of currently available NMBAs.

PORC occurred in 25–50% of procedures lasting <90 min (using intermediate-acting muscle relaxants) and in 25–50% of procedures lasting >90 min (using long-acting muscle relaxants). Finally, he showed that PORC could significantly reduce patients' response to hypoxia, reduce oesophageal sphincter tone and increase episodes of aspiration, thereby increasing the possibility of postoperative pulmonary complications. He concluded that failure to monitor neuromuscular response objectively after using muscle relaxants represents substandard care.

### A binding agent that reverses neuromuscular blockage

Given the problems outlined by Jørgen Viby-Mogensen, I was very interested to hear about the talk by Bertrand Debaene, France, on new muscle relaxants in development. I was also interested in the poster by Bom *et al.* at the ASA meeting (Rapid reversal of rocuronium-induced neuromuscular block by Org 25969 is independent of renal perfusion. ASA Meeting Abstracts, A-1158), as well as his presentation on the same subject at the recent joint meeting of Phys Soc and Pharm Soc in Manchester.

Muscle relaxants should ideally have both a rapid onset and a rapid offset, particularly with respect to intubation, but Debaene showed that some patients still have residual paralysis 120 min after a single intubating dose of an intermediate muscle relaxant. Thus, monitoring (e.g. acceleromyography) is required to ensure that the TOF (train-of-four) ratio is >0.9 before the patient is transferred to the recovery room (see box 2). Alternatively, a reversal agent (such as neostigmine) is given. However, neostigmine has little effect against profound block and can stimulate muscarinic and nicotinic receptors in other tissues. This is because neostigmine does not reverse muscle blockade, but acts as a competitive anticholinesterase, which effectively increases the agonist concentration to overcome the neuromuscular blockade.

#### Box 2 Monitoring the effects of NMBAs

During anaesthesia the effects of muscle relaxants must be monitored and one way to do this objectively is by monitoring neuromuscular transmission. This is commonly done by stimulating a peripheral nerve, such as the ulnar nerve and recording twitches in the adductor pollicis muscle of the thumb, a technique well known to many physiologists.

The most common pattern of stimulation consists of a train of four (TOF) stimuli, usually at 2Hz, 0.2 msec duration and 500 msec apart, potentially eliciting four muscle twitches (T1-T4). The response gives a crude indication of the degree of neuromuscular blockade achieved: when 75% of postjunctional acetylcholine (Ach) receptors are occupied by an NMBA the twitch magnitude starts to decrease and when there is 100% NMBA occupation no twitch occurs. The ratio of the amplitudes of T4:T1 indicates the degree of neuromuscular block. Disappearance of T4, T3, T2, T1 correspond to 75%; 80%, 90% and 100% NMBA occupancy of receptors.

Reference

Hughes S & Griffiths R (2002). Anaesthesia monitoring techniques. In Anaesthesia and Intensive Care Medicine, pp 477-480, The Medicine Publishing Company Ltd.

A new concept is to chemically sequester the neuromuscular blocking agent. In the case of the muscle relaxant rocuronium, this can be achieved with a tubular cyclodextrin (Org 25969), which encapsulates rocuronium, rather like a glove over a hand. Studies in healthy volunteers have shown that it is capable of reversing profound rocuronium blockade within 2–3 min. However, unlike neostigmine, it has no muscarinic or nicotinic effects. What is more the combined compound appears to pass safely through the kidneys into the urine. If this drug successfully gets through all phases of clinical research trials, it would be a great step forward in solving the problem of PORC, thereby increasing patient safety.

### Closed loop anaesthesia

As a physiologist, I am interested in feedback systems, and the idea of closed loop anaesthesia sounded fascinating. In closed loop control of anaesthesia, a computer program maintains the targeted effect (i.e. the set point defined by the anaesthetist) by adapting the amount of the different drugs administered. The anaesthetist only takes over if a major problem occurs. The rationale is that computers are superior to humans in terms of sustained attention, vigilance and prolonged decision making.

However, according to Michel Struys (Belgium), controller reliability strongly depends on the reliability of the physiological signal being measured. Unfortunately, depth of anaesthesia is difficult to measure and surrogate measures, such as blood pressure or muscle activity, may be used as the controlled variable, but these have not proved totally reliable. Investigators have previously found disadvantages when using univariate indicators derived from the electroencephalogram (EEG). More recently, multivariate statistics have been used to combine various features of the EEG into a single index, the bispectral index (BIS©).

Professor Struys said that BIS correlates well with changes in the level of hypnosis produced by anaesthetics and sedatives and, compared with other monitoring systems, should result in less drug usage, lower costs and faster return to consciousness for patients. The major challenge now is to establish the safety, efficacy, reliability and use of closed loop anaesthesia under extreme clinical conditions.

### The good, the bad and the maybe

In his presentation James E Cottrell (SUNY, New York) considered the use of a number of drugs and techniques that may or may not act as brain protectants in neurosurgery.

**The good** Although it is not a powerful neuroprotectant, remacemide, a glutamate antagonist through N-

methyl D aspartate (NMDA) channel blockade, was effective in retaining patients' ability to learn after coronary artery bypass surgery, as evidenced by neuropsychological tests. Professor Cottrell then pointed out that sodium influx is the first step in the ischaemic cascade and that truncating the initial steps of the cascade reduces the damage done by downstream events. Lidocaine, which has demonstrated neuroprotective properties, both *in vivo* and *in vitro*, blocks sodium influx and may reduce post-ischaemic injury by blocking apoptotic cell death via cytochrome C release and caspase-3 activation.

Another approach to neuroprotection is to pre-condition the brain with pre-operative hyperbaric oxygen or erythropoietin (EPO). According to Professor Cottrell the most impressive trial of a known pre-conditioning agent used erythropoietin, which is endogenously produced in the brain after hypoxic or ischaemic insults. Under normal circumstances, EPO increases the production of erythrocytes by preventing their apoptotic self destruction during differentiation. In the brain EPO is produced primarily by astrocytes in the ischaemic penumbra, where there is also an up-regulation of EPO receptors. According to Professor Cottrell EPO stimulates 'proteins of repair, diminishes neuronal excitotoxicity, reduces inflammation, inhibits neuronal apoptosis and stimulates both neurogenesis and angiogenesis subsequent to experimental ischaemic, hypoxic and toxic injury'. EPO also improved neurological outcomes and mental function. Professor Cottrell suggested that, assuming it gets through all its clinical trial development, EPO may eventually prove to be a very good prophylactic, pre-conditioning neuroprotectant, if administered 24–48 h before surgery.

**The bad** Professor Cottrell discussed a number of anaesthetic and adjuvant drugs, currently in use, but which have had disappointing effects as neuroprotectants. These included nitrous oxide, ketamine, nimodipine and tirilazid. Based on a wide variety


Scotland's other national drink, meant to vitalise, in too close proximity to the Euroanaesthesia 2003 sign *(Photo: David Murray)*

of studies, none of these agents were felt to exert significant neuroprotective effects. At a technical level he also indicated that post-operative mild hypothermia was not advantageous in head injury patients and might only delay neuronal death subsequent to an ischemic event.

**The maybe** Professor Cottrell reviewed a number of promising techniques and drugs. Low normothermia (36ºC) may be used in both the neuro and cardiac ICU to protect non-ventilated patients against infection and subsequent fever, which is strongly associated with a poor outcome. There is also accumulating evidence that prophylactic mild hypothermia offers a neuroprotective effect, since early cooling may have the potential to reduce ischaemic injury that is still developing.

Magnesium blocks both ligand and voltage dependant calcium entry into cells, but laboratory evidence indicates that pre-ischaemic magnesium administration is much more protective than post-ischaemic administration, which would probably limit its usefulness. However, a prospective, randomized trial of prophylactic magnesium in cardiac surgery patients is currently in progress.

Finally, Professor Cottrell stated that the inert gas xenon, an NMDA receptor antagonist, has shown some neuroprotective effects in animal studies, including improved neurocognition.

## No patient shall be harmed by anaesthesia

A cynic might say that we are still no closer to understanding how anaesthetics really work than we were 50 years ago, but anaesthesia safety has improved markedly over recent decades and has become institutionalized, according to Jeffrey Cooper (USA). The main contributions to anaesthetic safety have been leadership, research on error, safety prioritization, better technology, drug safety, and a safety culture. Institutionalization of anaesthetic safety has evolved through national safety committees, anaesthetic patient safety foundations, studies of closed claims, establishment of standards and protocols, etc. Dr Cooper said that challenges remain as patients are now older and sicker, procedures are more challenging, and there is pressure for anaesthetists to work faster and surgeons to be more productive.

To meet the new pressures and to maintain and continue safety improvements, Dr Cooper stressed the need to compare anaesthetic safety measures with those of high-risk organizations (HROs), which are intrinsically risky, but which have low failure rates, e.g. the flight deck of an aircraft carrier. The key principles to adopt from HROs include: a top-down commitment to safety; optimized structures and procedures; intensive training (operations and simulations); maintaining an active safety culture; learning from accidents and incidents; and teamwork by anaesthesiologists, surgeons and nurses. In summary, ensuring safety is a never-ending process, but the goal must be that no patient shall be harmed by anaesthesia.

## Postscript

In conclusion, we still don't really know how anaesthetics work, but patient safety is a primary concern and new drugs and techniques to aid more rapid recovery are probably of great interest to all concerned. From my point of view the amount of applied physiology and pharmacology makes reporting on anaesthesia profoundly interesting in its own right. A detailed report of the ASA conference can be found in ***aspects in anesthesia online*** (http://www.organon-conferences.com/ASA2003).

Bill Winlow
*Prime Medica Ltd, Knutsford, Cheshire*

# The exciting mitochondrion

Evidence is emerging that mitochondria play an important role in modulating the excitability of muscle and other cells. Not bad for an organelle that may have started out as a bacterium 'adopted' by primordial cells

George Stephenson (left) and Niels Ørtenblad

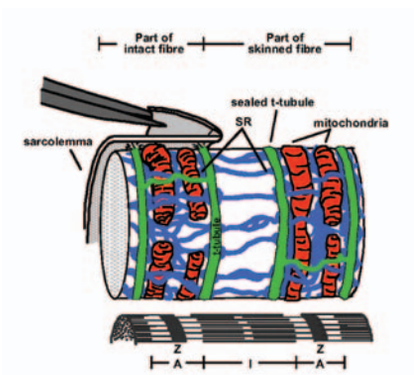



Figure 1. Schematic representation of preparing an 'inside out' skeletal muscle fibre and showing the relative position of mitochondria (red) with respect to the t-system (green), sarcoplasmic reticulum (blue) and the myofibrillar component (black) in rat skeletal fibres. Note that paired long mitochondria are transversely located at the I-band level wrapped around the contractile apparatus and in contact with sarcoplasmic reticulum but clearly separated from t-tubules (after Ørtenblad & Stephenson, 2003).

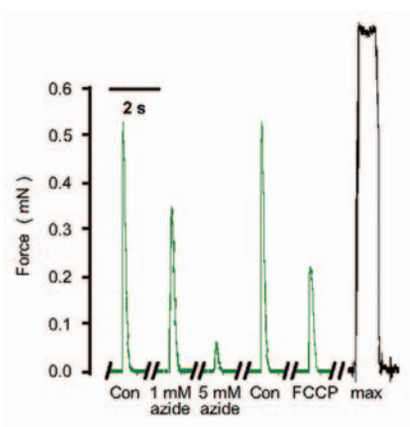



Figure 2. Representative action-potential induced force responses in an 'inside out' fast-twitch muscle fibre preparation of the rat in response to electrical stimulation under control conditions (con) and in the presence of azide ( 1 and 5 mM) and FCCP (1 μM). The last force response (max) was obtained when the preparation was maximally activated in a strongly $Ca^{2+}$-buffered solution ([$Ca^{2+}$] 30 μM) (traces from Ørtenblad & Stephenson, 2003).

The mitochondrion has been long known as the powerhouse of the eukaryotic cell supplying most of the necessary ATP to keep it alive (Lehninger, 1965). More recent studies have shown that the mitochondrion also plays prominent roles in the regulation of heat production (Palou *et al*. 1998), formation of oxygen radicals (Duranteau *et al*. 1998), calcium signalling (Pozzan *et al*. 2000), glucose homeostasis (Maechler & Wohlheim, 2000), oxygen sensing (Duchen, 2000; Chandel & Schumacker, 2000) and apoptosis (Newmeyer & Ferguson-Miller, 2003).

A recent study from our laboratory (Ørtenblad & Stephenson, 2003) has shown the mitochondrion may also regulate the excitability of the skeletal muscle fibre by a mechanism that is not dependent on changes in the intracellular levels of ATP, pH, $Mg^{2+}$ or $Ca^{2+}$. In this study, the ATP-producing ability of mitochondria was impaired with three molecularly diverse and commonly used mitochondrial inhibitors (azide, oligomycin and FCCP). When these mitochondrial antagonists were applied to a fully excitable 'inside out' rat muscle fibre preparation, where the composition of the myoplasmic environment was controlled with respect to [ATP], [$Ca^{2+}$], [$H^+$], [$Mg^{2+}$] and other diffusible substances, the excitability of the preparation decreased in a dose-dependent and reversible fashion. The 'inside out' excitable muscle fibre preparation was developed in our laboratory based on the 'mechanically skinned' fibre preparation first introduced by Natori in 1954 (Natori, 1972), in which the sarcolemma is removed by microdissection under oil, leaving the cellular structure of the muscle fibre otherwise intact. In this preparation the transverse tubular (t-) system, characteristic of skeletal (and cardiac) muscle fibres, pinches off and seals off as the surface membrane is removed (Lamb *et al*. 1995; Launikonis & Stephenson, 2001). The t-system forms the major interface between the cell and its extracellular environment and, when sealed, it repolarises if the preparation is placed in a solution mimicking the myoplasmic environment (Lamb & Stephenson, 1990; 1994). This is because the $Na^+$-$K^+$ pumps located in the t-system re-establish the [$Na^+$] and [$K^+$] gradients across the sealed t-system membranes. The t-system can then be depolarised either by ion substitution or by electrical stimulation triggering propagated action potentials (Posterino *et al*. 2000). The t-system depolarisation induces $Ca^{2+}$ release from the sarcoplasmic reticulum (SR) subsequently activates the contractile apparatus just as it does in an intact muscle fibre. A cartoon of this 'inside out' muscle fibre preparation displaying the relative position of mitochondria with respect to the t-system, SR and the myofibrillar component in a mammalian skeletal muscle fibre is shown in Fig. 1. In Fig. 2 are presented typical action-potential induced twitch responses in one such 'inside out' rat muscle fibre preparation in the presence and the absence of azide. Several lines of evidence indicate that the decrease in the size of the twitch response in the presence of the three mitochondrial ATP-producion inhibitors was caused by reduced fibre excitability due to depolarisation of the t-system (see Ørtenblad & Stephenson, 2003).

This phenomenon, in which impairment of mitochondrial ATP-producing function leads to graded depolarisation of the plasma membrane, reduced excitability and consequently reduced ATP consumption, is physiologically important because it is likely to play a key role in protecting the cellular ATP pool and thus safeguarding the cell from irreversible ATP-depletion induced injury. There are many observations of acute plasma membrane depolarisation during metabolic stress in several other cell types including

cardiac fibres (Hasin & Barry, 1984), neurons (Buckler & Vaughan-Jones, 1998) glial cells (Brismar & Collins, 1993) and endothelial cells (Park *et al*. 2002). It is highly probable that a mechanism similar to that uncovered with the 'inside out' skeletal muscle fibre preparation is at work in most cells, providing the feed-back loop to maintain the balance between cell capacity for ATP production and ATP utilization.

The mechanism by which the inhibition of mitochondrial ATP-producing function causes depolarisation of the plasma membrane in the t-system is not known. It is probable that a chemical messenger is involved in the communication between the mitochondria and the t-system because there is no continuity or tight physical coupling between mitochondria and the t-system to facilitate a more direct type of interaction. Also, in accord with this proposition, toad muscle fibre preparations, where mitochondria are not located as closely to the t-system as in mammalian muscle fibres, were found to be less sensitive to the mitochondrial inhibitors tested than the rat fibres.

Previous observations on intact cardiomyocytes (Duranteau *et al*. 1998) showed that azide reversibly increased the production of reactive oxygen species (ROS) by the mitochondria and in parallel depressed myocyte contractility, as in the study on 'inside-out' rat skeletal fibres (Fig. 2). Hence, the mechanism by which impairment of ATP-producing capacity of mitochondria causes depolarisation of the plasma membrane may involve ROS production in the mitochondria. ROS would diffuse out of the mitochondria and act on membrane channels increasing the relative membrane permeability to $Na^+$ compared to that of $K^+$ as suggested in our experiments (Ørtenblad & Stephenson, 2003). A very similar process of mitochondria-controlled plasma membrane excitability to that described by us has been very recently found to operate in brain stem motoneurons (Bergmann & Keller, 2003). Also, Isaeva & Shirokova (2003) have recently shown that application of various mitochondrial inhibitors led to the loss of mitochondrial $Ca^{2+}$ and promoted spontaneous $Ca^{2+}$ release from the SR. It is then possible that ROS generated in the mitochondria during metabolic stress would also act on the SR $Ca^{2+}$-release channels. A cross-talk between mitochondria and the sarcoplasmic reticulum would further support the idea that mitochondria play a much more active role than previously thought in modulating excitation-contraction coupling in skeletal muscle fibres.

Here it has been argued that ROS may play a critical role in facilitating the cross-talk between mitochondria and the t-system and between mitochondria and SR. However, one cannot exclude the possibility that other factors produced in the mitochondrion when its ATP-production function is impaired act as messengers between the mitochondria and other cellular membranes because there is clear evidence that many chemical messengers produced in the mitochondria can modulate cellular activity (Duchen, 2000).

Whatever the precise pathway of mitochondrial signalling to the plasma membrane may be, the finding that the mitochondrion could play a role in determining the excitability of the muscle cells should further transform this organelle into a fascinating object of study by excitable tissue physiologists.

D George Stephenson
*Niels Ørtenblad

*The Muscle Research Group, Department of Zoology, La Trobe University, Melbourne, Victoria, Australia*

**Institute of Sports Science and Clinical Biomechanics University of Southern Denmark, Odense, Denmark*

## References

Bergmann F & Keller BU (2003). Impact of mitochondrial inhibition on excitability and cytosolic $Ca2^+$ levels in brain stem motoneurons from mouse. J Physiol DOI: 10.1113/053900.

Brismar T & Collins VP (1993). Effects of external cation concentration and metabolic inhibitors on membrane potential of human glial cells. J Physiol 460, 365-383.

Buckler KJ & Vaughan-Jones RD (1998). Effects of mitochondrial uncouplers on intracellular calcium, pH and membrane potential in rat carotid body type I cells. J Physiol 513, 819-833.

Chandel NS & Schumacker PT (2000). Cellular oxygen sensing by mitochondria: old questions, new insight. J Appl Physiol 88, 1880-1889.

Duchen, MR (2000). Mitochondria and calcium: from cell signalling to cell death. J Physiol 529, 57-68.

Duranteau J, Chandel NS, Kulisz A, Shao Z & Schumacker PT (1998). Intracellular signaling by reactive oxygen species during hypoxia in cardiomyocytes. J Biol Chem 273, 11619-11624.

Hasin Y & Barry, WH (1984). Myocardial metabolic inhibition and membrane potential, contraction, and potassium uptake. Am J Physiol 247, H322-H329 .

Isaeva EV & Shirokova N (2003). Metabolic regulation of $Ca^{2+}$ release in permeabilized mammalian skeletal msucle fibres. J Physiol 547, 453-462.

Lamb GD & Stephenson DG (1990). Calcium release in skinned muscle fibres of the toad by transverse tubule depolarization or by direct stimulation. J Physiol 423, 495-517.

Lamb GD & Stephenson DG (1994). Effects of intracellular pH and $[Mg^{2+}]$ on excitation-contraction coupling in skeletal muscle fibres of the rat. J Physiol 478, 331-339.

Lamb GD, Junankar PR & Stephenson DG (1995). Raised intracellular $[Ca^{2+}]$ abolishes excitation-contraction coupling in skeletal muscle fibres of rat and toad. J Physiol 489, 349-362.

Launikonis BS & Stephenson DG (2001). Effects of membrane cholesterol manipulation on excitation-contraction coupling in skeletal muscle of the toad. J Physiol 534, 71-85.

Lehninger AL (1965). The mitochondrion: molecular basis of structure and function. 2nd print. New York: WA Benjamin.

Maechler P & Wollheim CB (2000). Mitochondrial signals in glucose-stimulated insulin secretion in the beta cell. J Physiol 529, 49-56.

Natori R (1972). Some physiological aspects of internal membrane of skeletal muscle fibres. Jikeikai Med J 19, 51-64.

Newmeyer DD & Ferguson-Miller S (2003). Mitochondria: releasing power for life and unleashing the machineries of death. Cell 112, 481-490.

Ørtenblad N & Stephenson DG (2003). A novel signalling pathway originating in mitochondria modulates rat skeletal muscle membrane excitability. J Physiol 548, 139-145.

Palou A, Pico C, Bonet ML & Oliver P (1998). The uncoupling protein, thermogenin. Int J Biochem Cell Biol 30, 7-11.

Park KS, Jo I, Pak K, Bae SW, Rhim H, Suh SH, Park J, Zhu H, So I & Kim KW (2002). FCCP depolarizes plasma membrane potential by activating proton and $Na^+$ currents in bovine aortic endothelial cells. Pflügers Arch 443, 344-352.

Posterino GS, Lamb GD & Stephenson DG (2000). Twitch and tetanic force responses and longitudinal propagation of action potentials in skinned skeletal muscle fibres of the rat. J Physiol 527, 131-137.

Pozzan T, Magalhaes P & Rizzuto R (2000). The comeback of mitochondria to calcium signalling. Cell Calcium 28, 279-283.

# Cortical control of human jaw muscles: bilateral but not symmetrical

Transcranial magnetic stimulation is revealing new details of the cortical control of human jaw muscles

Michael Nordstrom (left) and Sophie Pearce

Movements of the jaw during everyday activities such as chewing and speech require the bilateral co-ordination of muscles acting on the mandible. Control of these movements needs to be extremely precise to bring the teeth reliably into contact on each chewing stroke (with sub-millimetre tolerances), and to avoid damaging vulnerable oral structures such as the tongue and cheeks. Three muscles innervated by the trigeminal nerve control jaw closing and two main muscles control jaw opening on each side. Although the muscles on each side are usually activated together, the jaw-closers such as masseter can be controlled relatively independently when the situation demands (Butler *et al.* 2001). While voluntary control of the jaw muscles is mediated by the motor cortex, there are differences with the more widely studied limb muscles. For example, while fast, monosynaptic pathways from the motor cortex to motoneurons (corticomotoneuronal, or CM cells) are known to be involved in the precise, selective control of hand muscles, the evidence for the existence of such cells in the trigeminal system has been largely indirect. Furthermore, motoneurons of hand muscles receive a corticospinal projection almost exclusively from the contralateral hemisphere, while corticobulbar neurons from each hemisphere project to the vicinity of the trigeminal motor nuclei on both sides (Kuypers, 1958).

This arrangement poses several questions. What contribution does this bilateral cortical control system make to activation of jaw muscles? If CM cells exist in this bilateral system, how are they organised?

Figure 1 illustrates several possibilities for the cortical control of masseter motoneurones. While there is indirect evidence that axons of single CM cells branch to innervate jaw muscle motoneurons on both sides of the body (Carr *et al.* 1994), these neurones (green in Fig. 1) could not directly mediate selective activation of left and right muscles. Most textbooks describe the corticobulbar projections as bilateral and symmetrical, implying that each hemisphere makes a comparable contribution to control of the jaw muscles. The dual innervation undoubtedly helps to preserve control of masticatory muscles following unilateral stroke (Cruccu *et al.* 1988), but do the two hemispheres play distinct roles in controlling the jaw muscles on each side of the body?

These questions can be investigated in humans using a technique known as transcranial magnetic stimulation (TMS), in which a brief magnetic field is induced by a stimulating coil placed on the scalp over the motor cortex. This painless, non-invasive technique activates corticospinal or corticobulbar neurons within the motor cortex, which in turn elicit a response in the muscles of interest that can be detected using electromyography (EMG).

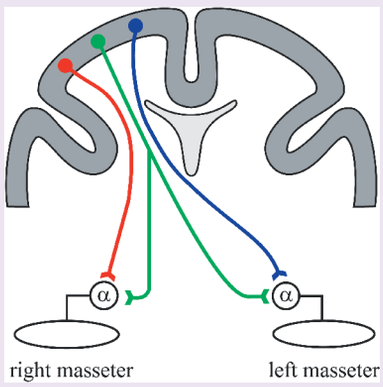



Figure 1. Schematic depicting three possibilities for the innervation of masseter motoneurons by corticobulbar neurons in the motor cortex of one hemisphere. Corticobulbar neurons with exclusively contralateral (blue), exclusively ipsilateral (red) and bilateral (green) projections are shown.

Early studies using surface EMG and TMS reported fast-conducting excitatory projections from the motor cortex to the masseter motoneuron pools on both sides: however, the circular coil used in these studies may have activated both hemispheres simultaneously (Cruccu *et al.* 1989). When we confined the stimulus to one hemisphere by using a figure-8 TMS coil, the response evoked in masseter was still bilateral, and was ~40% larger in the contralateral muscle (Butler *et al.* 2001). The response latency on each side is ~7 ms, which is consistent with a CM projection to both muscles from one hemisphere. We also showed that selective activation of the masseter muscle on one side during a unilateral bite was mediated by corticobulbar neurons in the contralateral but not the ipsilateral hemisphere (Butler *et al.* 2001). Clearly the two hemispheres have distinct roles in this task.

We suggest that selective activation of one masseter is accompanied by reduced excitation of CM cells in the contralateral hemisphere which branch to innervate both masseter motoneuron pools (the green projection in Fig. 1). The larger contralateral responses to focal TMS and their task-dependence point to a second population of CM cells with exclusively contralateral projections to masseter motoneurons (blue projection in Fig. 1). We found no evidence for the existence of the red CM cells.

With surface EMG studies such as these, the evidence for monosynaptic excitation of trigeminal motoneurons by CM cells is strong, but not conclusive, as it is based on latency measures and assumptions about conduction velocities of the axons involved. To provide unambiguous evidence of CM projections to

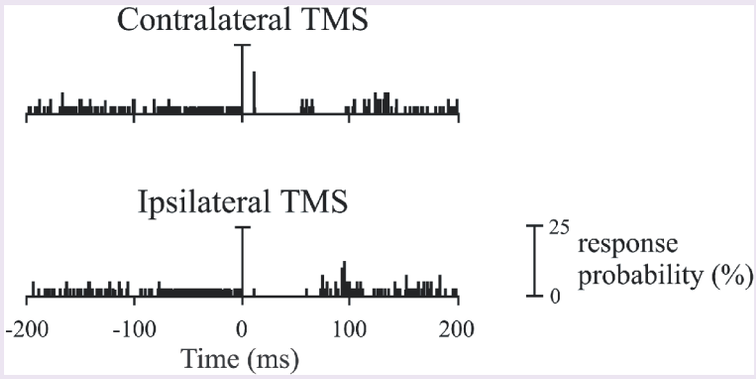



Figure 2. Responses of a single masseter motor unit to focal TMS applied to either hemisphere. The subject maintained a steady voluntary discharge of the motor unit while 40 TMS were given, at unpredictable times. The peri-stimulus histogram shows the probability of motor unit discharge at various times relative to the stimulus (given at time 0) for the 40 TMS trials. Following contralateral TMS (upper) there was an increased probability of motor unit firing at ~7 ms (i.e. the motor unit was excited by the stimulus). In contrast, following ipsilateral TMS (lower) there was no short-latency excitation. TMS of either hemisphere suppressed motor unit discharge for up to 100 ms by mechanisms that are still under investigation, but probably include cortical inhibition. Adapted from Pearce et al. 2003.

motoneurons it is necessary to record responses of single motor units to TMS. A motor unit consists of a single motoneuron, its axon and the skeletal muscle fibres it innervates. Motor unit activity can be detected in humans by fine-wire electrodes inserted into the muscle. Because of the secure 1:1 transmission of the action potential between nerve and muscle, this technique gives information about the discharge pattern of a single motoneuron in the brainstem (in the case of the jaw muscles).

Single motor unit recordings from masseter and digastric muscles during weak voluntary contractions confirm the existence of CM projections to trigeminal motoneurons (Gooden *et al.* 1999; Pearce *et al.* 2003), and show that single motor units are differentially controlled by the two hemispheres. An example of the responses of a masseter motor unit to focal TMS of the contralateral and ipsilateral hemisphere is shown in Fig. 2. As in this example, most of the masseter motor units were excited at monosynaptic latency only by TMS of the contralateral hemisphere. A minority (25%) were excited at monosynaptic latency by TMS of either hemisphere. The excitatory response to contralateral and ipsilateral TMS (when present) was very brief (~1.5 ms), and consistent with production of a monosynaptic excitatory post-synaptic potential in the masseter motoneuron by the corticobulbar neurons activated by TMS. This narrow peak is conclusive proof for CM cell projections to masseter. At low biting forces, most of the direct excitation of masseter comes from the contralateral motor cortex. Many masseter motor units active at low forces do not receive excitatory inputs from the ipsilateral hemisphere. This would contribute to the smaller response to TMS seen in the ipsilateral muscle with surface EMG. In contrast, most digastric motor units receive excitatory inputs from both hemispheres (Gooden *et al.* 1999). These differences presumably contribute to the more independent activation of the masseter muscles on each side during functional tasks than the symmetrical pattern observed for the digastric muscles.

The functional organization of the corticobulbar projection to the trigeminally innervated jaw muscles is complex. The traditional model, based on anatomical evidence, of bilateral and symmetrical corticobulbar projections is no longer tenable. We have demonstrated that motor cortices of both hemispheres are involved in the control of trigeminal motoneurons, although the contralateral hemisphere has a greater effect overall, particularly at low forces. The two hemispheres play distinct roles in the control of ipsi- and contralateral muscles, and this differs for jaw-closers and openers. The cortical control of all motor units in a muscle is not uniform. Some motor units are excited exclusively from the contralateral hemisphere, while others receive bilateral excitatory inputs. This complexity in the corticobulbar innervation of jaw muscles may assist controlled biting on one side when food is held between the teeth. These observations suggest that functional deficits in masticatory muscles following unilateral stroke should be greater for muscles contralateral to the lesion. This has been shown for maximal voluntary activation of masseter (Cruccu et al. 1988), but more subtle deficits in fine control of the contralateral jaw muscles would also be expected, although these have not been explored in patients.

Sophie L Pearce
Michael A Nordstrom
*Discipline of Physiology*
*School of Molecular & Biomedical Science*
*University of Adelaide, Australia*

## References

Butler SL, Miles TS, Thompson PD & Nordstrom MA (2001). Task-dependent control of human masseter muscles from ipsilateral and contralateral motor cortex. *Exp Brain Res* 137, 65-70.

Carr LJ, Harrison LM & Stephens JA (1994). Evidence for bilateral innervation of certain homologous motoneurone pools in man. *J Physiol* 475, 217-227.

Cruccu G, Berardelli A, Inghilleri M & Manfredi M (1989). Functional organization of the trigeminal motor system in man. A neurophysiological study. *Brain* 112, 1333-1350.

Cruccu G, Fornarelli M & Manfredi M (1988). Impairment of masticatory function in hemiplegia. *Neurology* 38, 301-306.

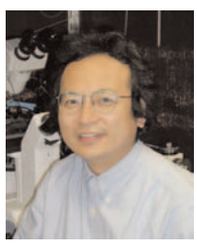
Gooden BR, Ridding MC, Miles TS, Nordstrom MA & Thompson PD (1999). Bilateral cortical control of the human anterior digastric muscles. *Exp Brain Res* 129, 582-591.

Kuypers HGJM (1958). Corticobulbar connexions to the pons and lower brain-stem in man. *Brain* 81, 364-388.

Pearce SL, Miles TS, Thompson PD & Nordstrom MA (2003). Responses of single motor units in human masseter to transcranial magnetic stimulation of either hemisphere. *J Physiol* 549, 583-596.

# Flavoprotein autofluorescence

Spectroscopic measurements of cellular autofluorescence have a 50 year history, but still have much to give. Here Katsuei Shibuki and Ryuichi Hishida describe an underestimated technique for functional brain imaging

Katsuei Shibuki (left) and Ryuichi Hishida

Optical recording of neural activities is a powerful method for investigating physiological functions of the brain. The technique can be classified into two types: those using extrinsic dyes sensitive to membrane potential, $Ca^{2+}$ or pH, and those using endogenous signals (Ebner & Chen, 1995). The latter includes so-called intrinsic signal recording based on the intimate coupling between neural activities and oxygen consumption (Frostig *et al*. 1990).

Although the signal amplitude is small, this method is widely used because it is free from the various problems accompanying the usage of extrinsic dyes. Flavoprotein autofluorescence is another endogenous signal that might be applicable for functional brain imaging (Chance *et al*. 1962), but has not been applied for functional brain imaging as widely as the intrinsic signal.

About three years ago, we began optical recording *in vivo*, and used voltage-sensitive dyes for investigating the mechanisms of learning and memory. Unfortunately, we discovered that this method was too delicate for our purposes. We had thought that neural activities in the whole brain might be recorded as $Ca^{2+}$ signals, because $Ca^{2+}$ imaging is useful in brain slices. For testing this idea, the surface of the cerebral cortex in an anaesthetized rat was stained with various $Ca^{2+}$ indicators, and $Ca^{2+}$ imaging was performed in the slices obtained. To our surprise, green autofluorescence of the slices showed a marked increase in response to electrical stimulation, although the $Ca^{2+}$ indicators were poorly infiltrated into the brain.

Investigation of previous studies lead us to conclude that the responses were derived from the autofluorescence of flavoproteins, one of the components of the electron transfer system in mitochondria (Chance *et al*. 1962; Rosenthal & Jöbsis, 1971; Benson *et al*. 1979). A rise in intracellular $Ca^{2+}$ triggered by neural activities stimulates oxygen consumption in mitochondria. Activation of the electron transfer system in mitochondria then converts the flavoproteins into an oxidized form, which emits green autofluorescence in blue light. Therefore, by measuring changes in green autofluorescence, we can visualize neural activities. This method turned out to be quite useful for functional brain imaging, not only in slices but also in the whole brain in anesthetized rats (Shibuki *et al*. 2003). The amplitude of the signal ($\Delta F/F$) was 10-100 times larger than that of intrinsic signal recording. The fluorescence signal appeared only 0.1-0.2 s after, and reached a peak only 0.6-0.8 s after, the onset of stimulus *in vivo*. The signal faded slowly, and spontaneous recovery from bleaching was observed when the excitation light was turned off for a while. These characteristics appear suitable for investigating the mechanisms of learning and memory in the whole brain.

When we first showed our data at scientific meetings, optical recording specialists posed many sceptical questions. This was because flavoprotein autofluorescence had already been known and tested over many years, and the tentative conclusion had been that it might not be good enough for functional brain imaging. So, if it was as good as suggested by our data, why had it not been widely used? We can think of a number of reasons.

First, the body weight of animals used for the recording is critical. We used rats for autofluorescence imaging. We also confirmed that it works well in mice (unpublished data). However, good results were not obtained in cats, dogs or human subjects in preliminary experiments (Table 1).

Autofluorescence imaging success in some animal species is partly explained by species differences in metabolic rates per body weight. This parameter is inversely proportional to a quarter power of the body weight (Gillooly *et al*. 2001). Next, motion artefacts produced by breathing or heart beats are more problematic in large animals. Further, excitation or the emission light

Table 1. Flavoprotein autofluorescence imaging of cortical activities in various species

| Species | Body weight (g) | Response to natural stimulation | Response to electrical stimulation |
|---|---|---|---|
| Human | $6 \times 10^4$ | not detected | not detected |
| Dog | $1 \times 10^4$ | not detected | good |
| Cat | $3 \times 10^3$ | not clear | not tested |
| Rat | $3 \times 10^2$ | good | good |
| Mouse | $3 \times 10^1$ | good | good |

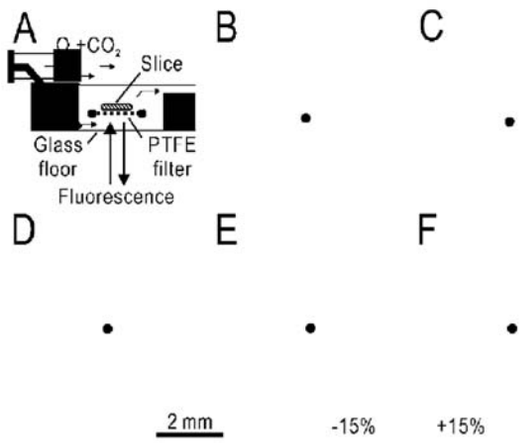



Figure 1. Flavoprotein autofluorescence and oxygen supply in cortical slices
A, Recording chamber. A slice obtained from a rat auditory cortex was placed in a recording chamber perfused with oxygenated medium. B, Pseudocolour images of the green autofluorescence change (ΔF/F) in blue light after electrical stimulation (20 Hz for 1 s at 300 μA) applied at layer V (black spots). Images 2 s after the stimulus onset are shown. C, Response of the same slice shown in B. In this experiment, the slice was directly placed on the glass floor of the recording chamber. D, Control autofluorescence response. In this experiment, the oxygenated medium was pumped into the recording chamber through stainless steel tubing. E, Autofluorescence responses of the same slice shown in D. The oxygenated medium was pumped through silicon rubber tubing. F, Recovery of autofluorescence responses after stainless steel tubing was used again. Data in D-F were obtained in the same slice.

used for fluorescence measurement can more easily penetrate through a small brain. Therefore, it is understandable if flavoprotein autofluorescence imaging in animals larger than rats does not produce good results.

The second crucial factor for autofluorescence imaging is the oxygen supplied to the brain tissue, especially in the experiments using slices. We tried to keep the oxygen pressure at the surface of slices emitting autofluorescence as high as possible. In our experiments, slices were placed on a hydrophilic polytetrafluoroethylene (PTFE) membrane filter, which is permeable to oxygenated medium (Fig. 1A). This porous filter becomes transparent in water, because the refractive index of the material is almost the same as that of water.

Although autofluorescence responses were clearly recorded in a slice placed on the PTFE filter (Fig. 1B), the same slice directly placed on the glass floor of the recording chamber showed only faint responses (Fig. 1C). The small responses remaining near the pial surface of the slice (Fig. 1C) could be maintained by the diffusion of oxygen from the pial surface. Moreover, we need to be aware that permeability to oxygen differs among various materials. If oxygenated medium was pumped into the recording chamber through stainless steel tubing, clear autofluorescence responses were recorded in a slice placed on the PTFE filter (Fig. 1D,F). However, the same slice showed no response when the medium was pumped through silicone rubber tubing (Fig. 1E). In this experiment, the oxygen level in the recording chamber was reduced to the level of the air, because the silicon rubber tubing is permeable to oxygen.

There are also other important reasons: one is the choice of anaesthetic, because some anaesthetics severely suppress mitochondrial metabolism (Cohen, 1973). We obtained good results using urethane as an anaesthetic but not in rats anaesthetized with pentobarbital. Progress in the development and design of experimental equipment is also important. Obviously, we can today use better cameras and fluorescence microscopes than those used by pioneers in the field of evaluating flavoprotein autofluorescence for functional brain imaging.

Recently, new GFP-based fluorescence probes have been developed for functional brain imaging (Miyawaki *et al*. 1997). The green fluorescence signals derived from endogenous flavoproteins should be carefully distinguished from those derived from the new probes. However, if both signals are well distinguishable, flavoprotein autofluorescence could be used as a control signal giving information concerning whether the system works well or not.

We think flavoprotein autofluorescence imaging has been underestimated for a long time as a functional brain imaging technique. However, it is a workable method for investigating learning or memory in small animals, particularly in the visualization of cortical activities in mice.

Ultimately, though, the most convincing answer to those sceptical questions posed to us will be the results of future studies using this technique.

Katsuei Shibuki
Ryuichi Hishida
*Department of Neurophysiology, Brain Research Institute, Niigata University, Asahi-machi, Niigata, Japan*

## References

Benson RC, Meyer RA, Zaruba ME & McKhann GM (1979). Cellular autofluorescence - is it due to flavins? *J Histochem Cytochem* 27, 44-48.

Chance B, Cohen P, Jöbsis FF & Schoener B (1962). Intracellular oxidation-reduction states *in vivo*. *Science* 137, 499-508.

Cohen PJ (1973). Effect of anesthetics on mitochondrial function. *Anesthesiology* 39, 153-164.

Ebner TJ & Chen G (1995). Use of voltage-sensitive dyes and optical recordings in the central nervous system. *Prog Neurobiol* 46, 463-506.

Frostig RD, Lieke EE, Ts'o DY & Grinvald A (1990). Cortical functional architecture and local coupling between neuronal activity and the microcirculation revealed by in vivo high-resolution optical imaging of intrinsic signals. Proc Natl Acad Sci USA 87, 6082-6086.

Gillooly JF, Brown JH, West GB, Savage VM & Charnov EL (2001). Effects of size and temperature on metabolic rate. *Science* 293, 2248-2251.

Miyawaki A, Llopis J, Heim R, McCaffery JM, Adams JA, Ikura M & Tsien RY (1997). Fluorescent indicators for $Ca^{2+}$ based on green fluorescent proteins and calmodulin. *Nature* 388, 882-887.

Rosenthal M & Jöbsis FF (1971). Intracellular redox changes in functioning cerebral cortex. II. Effects of direct cortical stimulation. *J Neurophysiol* 34, 750-762.

Shibuki K, Hishida R, Murakami H, Kudoh M, Kawaguchi T, Watanabe M, Watanabe S, Kouuchi T & Tanaka R (2003). Dynamic imaging of somatosensory cortical activity in the rat visualized by flavoprotein autofluorescence. *J Physiol* 549, 919-927.

# Relax in a flash – shedding light on vascular smooth muscle photorelaxation

Recent research has shown that the ability of light to relax vascular smooth muscle is due to the photochemical release of NO from a rechargeable chemical 'store'. Studies of the recharging mechanism suggest that light-sensitive sources of NO are also likely to be present in other cell types

Eric Flitney

Vascular smooth muscle (VSM) relaxes when irradiated with either visible or ultra-violet (UV) light. This remarkable response, called 'photorelaxation', was first described by Robert Furchgott and his colleagues over 40 years ago (Furchgott *et al*. 1962).

Some 20 years later, in their landmark paper, Furchgott & Zawadski (1980) showed that certain vasodilators act on blood vessels by stimulating the endothelial cell lining to release a highly-diffusible, labile substance that relaxes VSM cells in the vessel wall.

This potent 'relaxing factor' was later shown to be nitric oxide (NO) (Palmer *et al*. 1987), synthesised in endothelial cells from the amino acid L-arginine by an enzyme called nitric oxide synthase, or NOS. Inevitably, comparisons were drawn between endothelium-dependent relaxations and photorelaxation. Some striking similarities were found and so it was suggested that photorelaxation might be due to a light-activated relaxing factor with properties akin to NO, or perhaps even to NO itself.

This was an attractive hypothesis and a relatively straightforward one to test. In the event, however, confusing reports appeared in the literature, some of which did not sit comfortably with this idea. First, vessels from which the endothelium had been removed would relax when exposed to light. Second, photorelaxation was reportedly enhanced in vessels from hypertensive animals, whereas endothelium-dependent relaxations were attenuated. Third, and most damaging of all, photorelaxation was shown to increase after blocking the enzyme that synthesises NO. (The last turned out to be a red herring when it was found that the NOS inhibitors used in these studies could release significant amounts of NO when exposed to light!)

Our recent studies of photorelaxation (Flitney & Megson, 2003) used functionally-intact segments of rat tail artery that were perfused at a constant flow rate and irradiated from time to time with either visible or UV light. The perfusion pressure was recorded continuously and vessels from rats with normal blood pressures were compared to those from a strain of animal that spontaneously develops high blood pressures, widely used as a model for human hypertension.

These experiments showed that irradiating an artery with visible light produced a transient relaxation: an initial, rapid loss of pressure that reversed fully during the period (6 min) of illumination. The vessel was then no longer able to respond to a second, identical period of irradiation given immediately after the first. However, we found that its sensitivity to light returned spontaneously when it was allowed to remain for a time in the dark. The recovery process, called 'repriming', displayed an absolute requirement for both endothelium-derived NO and tissue thiols.

Based upon these observations, we concluded that photorelaxation is due to the release of NO from a photosensitive chemical 'store', most likely one of the class of compounds called *S*-nitrosothiols (Megson *et al.* 1995; 2000).

The responses we obtained using UV light turned out to be more complex than those seen with visible light. These consisted of an initial rapid dilation followed by a partial reversal only, resulting in a residual level of reduced pressure that persisted for as long as the vessel remained illuminated. The form of the UV response suggested to us that it might be a composite one, made up of two vasodilator responses: a brief *phasic* component, superimposed on a *sustained* component.

This idea, illustrated in Fig. 1, was confirmed when it was shown that the two components behaved quite differently. The phasic element was indistinguishable from responses obtained using visible light: it too showed refractoriness and the repriming process displayed an absolute requirement for endothelium-derived NO. By contrast, the sustained component did not show refractoriness and it was not dependent upon endothelium-derived NO. Other

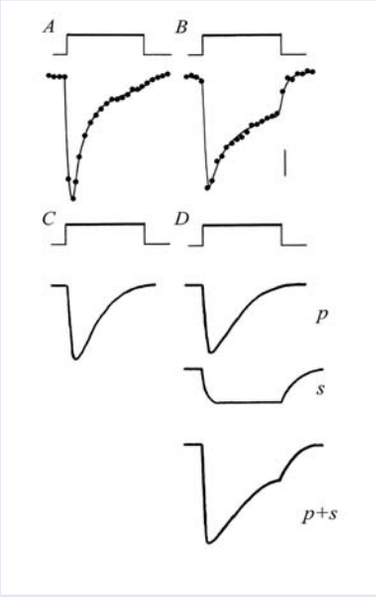



Figure 1. Time averaged recordings (n = 7) of photorelaxations elicited by visible light (A) and UV light (B). The form of the UV response can be explained if we postulate that it comprises a phasic (*p*) component, similar to the visible light-induced response (C) superimposed on a sustained (*s*) component (D)

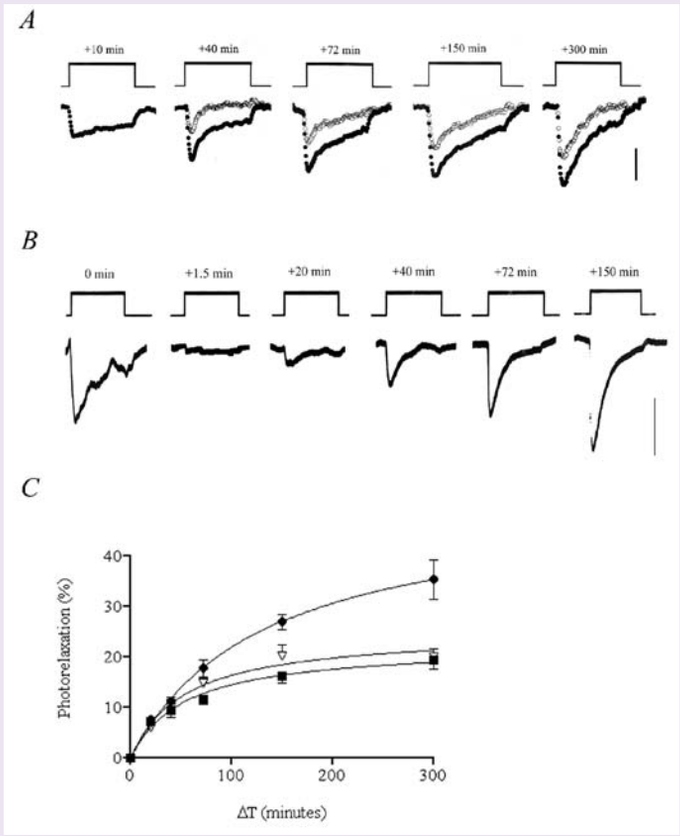



Figure 2. Spontaneous recovery of the phasic component (open circles) of UV-induced responses (A) and visible light-induced photorelaxation (B). Both sets of recordings made using vessels from normotensive animals. C. Time course of the recovery (repriming) of vessels from normotensive animals irradiated with visible light (upper curve, filled circles) compared with vessels from spontaneously hypertensive animals irradiated with *either* UV (phasic component, filled squares) *or* visible light (empty triangles). The latter two curves are not significantly different from one another, but both are significantly different from the uppermost (normotensive) curve

important differences emerged when vessels from normotensive rats were compared to those from spontaneously hypertensive animals. Thus, NO-mediated photorelaxation was attenuated in vessels from the hypertensive animals (Fig. 2), in line with similarly reduced endothelium-dependent relaxations, whereas the sustained component of the UV-induced response was enhanced.

These latest findings establish the importance of NO in the mechanism of photorelaxation and of the endothelium as the source of NO needed to fuel the repriming process. They also highlight the fact that the response to light is greatly influenced by the prior history of a vessel. The duration of the interval between successive periods of illumination is clearly an important factor. The rate of flow of fluid through a vessel will probably prove to be important as well, since shear stresses associated with flow enhance NO synthesis by endothelial cells. Thus, the extent to which the store becomes replenished in the dark, and hence the size of the next in a series of responses to light, will largely depend upon these two variables.

Some important questions about photorelaxation remain unanswered. What is the physiological significance of a molecular store of NO in VSM? Is it a re-usable resource, one from which NO can be released during periods of increased demand, perhaps by way of some as yet unidentified 'dark' reaction(s); or is it simply the by-product of a 'mopping-up' process designed to chemically inactivate excess NO? Does the photosensitive character of the store have any physiological significance?

The answer to this is probably not, since relatively few blood vessels will see the light of day. It seems much more likely that this is an unavoidable consequence of the chemical nature of the store. Of course, this is not to say that it is of no interest or has no value to physiologists. Quite the reverse in fact, because the ability to release NO virtually instantaneously inside cells at will provides us with an important analytical tool, analogous to our use of synthetic 'caged' compounds to elevate other physiologically-active ligands inside cells.

So do studies of photorelaxation have wider implications for cell physiology? It seems so. There is no reason to suppose that VSM cells are unique in containing a photosensitive store of NO. Indeed, from what we know of the probable chemical nature of the store and of the repriming mechanism, we can be reasonably certain that similar stores do exist elsewhere. This opens up exciting possibilities for future studies of NO-mediated phenomena in other cell types.

Eric Flitney
*School of Biology, Division of Cell & Molecular Biology*
*University of St Andrews, Scotland*

*(from March 2004: Cell & Molecular Biology, Feinberg Medical School of Northwestern University, Chicago, IL, USA)*

## References

Flitney FW & Megson, IL (2003). Nitric oxide and the mechanism of rat vascular smooth muscle photorelaxation. *J Physiol* 550, 819-828.

Furchgott RF, Ehrreich SJ & Greenblatt E (1961). The photoactivated relaxation of smooth muscle of rabbit aorta. *J Gen Physiol* 44, 499-519.

Furchgott RF & Zawadski JV (1980). The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. *Nature* 288, 373-376.

Megson IL, Flitney FW, Bates J & Webster R (1995). Repriming of vascular smooth muscle photorelaxation is dependent upon endothelium-derived nitric oxide. *Endothelium* 3, 39-46.

Megson IL, Holmes SA, Magid KS, Pritchard RJ & Flitney FW (2000). Selective modifiers of glutathione biosynthesis and 'repriming' of vascular smooth muscle photorelaxation. *Br J Pharmacol* 130, 1575-1580.

Palmer RMJ, Ferrige AG & Moncada S (1987). Nitric oxide release accounts for the biological activity of EDRF. *Nature* 327, 524-526.

# Airway liquid secretion and cystic fibrosis lung disease

Stephen Ballard describes recent studies into anion and liquid secretion in airways and discusses how inhibition of this process provides important insights into the pathogenesis of CF

Stephen Ballard

Persons afflicted with cystic fibrosis (CF) suffer from numerous maladies including pancreatic insufficiency, intestinal obstruction, and sterility (in males). However, it is the pulmonary complications of the disease that cause premature death and morbidity in the vast majority of cases.

CF lung disease is characterized by the production of a thickened airway mucus, impairment of mucociliary transport, unusually high susceptibility to microbial infection of the airways, and gradual degeneration of the lung due to a constant state of inflammation.

CF is caused by mutations in the gene that codes for the CFTR, a transmembrane protein that normally functions as a cAMP-regulated chloride channel. In the lung, the CFTR resides in the apical membranes of the serous cells of submucosal glands and the epithelial cells that line the airway surfaces.

Our laboratory focuses on the possible role that CFTR-mediated chloride and liquid secretion plays in the normal lung and how disruption of this process might lead to the pulmonary pathology seen in CF.

To better understand why chloride secretion might be important to normal airway function, we first looked at different airway regions to see if this process was localised in the lung. In the distal airways of the pig lung, whose morphology closely resembles the human lung, the basal rates of chloride secretion are far greater in the bronchi, the muscular thick-walled airways that express many submucosal glands, than in the bronchioles, the thin-wall compliant airways that are aglandular (Ballard *et al*. 1995). When the bronchi are exposed to glandular secretogogues, such as acetylcholine or substance P, the glands respond by vigorously secreting not only chloride but also bicarbonate which together drive the secretion of liquid by these tissues (Ballard *et al.* 1999, Trout *et al.* 2001).

Normally, when submucosal glands of the airways are stimulated, they secrete not only liquid from the serous cells but also gel-forming mucins from mucous cells. We reasoned that, if we selectively inhibited the liquid component of gland secretion and stimulated the glands to secrete, then mucin and fluid secretion would become uncoupled, leading to the secretion of a very thick, low-volume mucus. Indeed, when we pretreat pig bronchi with bumetanide, a loop diuretic that inhibits chloride secretion, and dimethylamiloride (DMA), a sodium-proton exchange inhibitor that blocks bicarbonate secretion, and then stimulate the airways with acetylcholine, the glands become impacted with mucin, replicating the earliest sign of CF airway disease (Fig. 1) (Inglis *et al.* 1998). The same anion secretion inhibitors also lead to the production of a thickened airway mucus with altered rheological properties; however, these changes alone are probably not adequate to impair mucociliary transport (Trout *et al.* 1998).

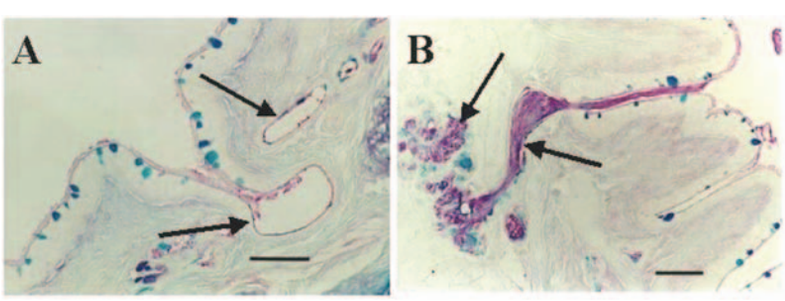



Figure 1. Effect of anion secretion inhibitors on mucin content of submucosal glands. A. Bronchus treated only with acetylcholine. B. Bronchus pretreated with bumetanide and DMA, to respectively inhibit chloride and bicarbonate secretion, prior to acetylcholine addition. Note that densely-staining mucins occlude the gland ducts when anion secretion inhibitors are present. Figure taken from Inglis *et al.*(1998).

Airway surface liquid (ASL) normally exists in two phases: a low viscosity 'sol' phase, which occupies the periciliary space, and a high viscosity 'gel' phase, which contains the gel-forming mucins and is usually excluded from the periciliary space. For mucociliary transport to function normally, the cilia of the surface epithelial cells must beat within the sol phase which is maintained by a balance of liquid secretion (originating from glands and probably from surface epithelium as well) and liquid absorption (driven by active sodium absorption across the surface epithelium). When blockers of chloride and bicarbonate secretion are used to disable liquid secretion in porcine tracheas *in vitro* mucociliary transport is nearly abolished (Ballard *et al*.2002) (Fig. 2). However, if the tissues are also exposed to benzamil, an inhibitor of epithelial sodium channels (ENaC) which mediate absorption, mucociliary transport is preserved at approximately one-half the control rate. When bumetanide and DMA are infused into an isolated, vascular perfused pig lung to block airway liquid secretion, the periciliary fluid becomes depleted, and the cilia are flattened between the dense mucus gel layer and the apices of the epithelial cells (Trout *et al.* 2003) (Fig. 3). Therefore, the impairment of mucociliary transport is likely to be due

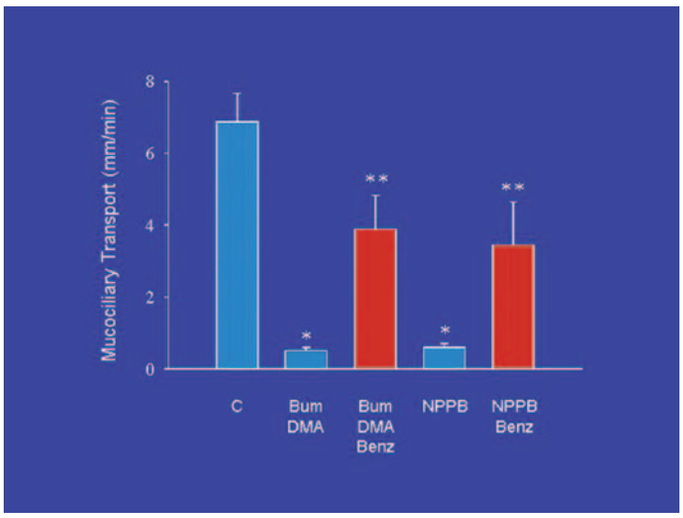



Figure 2. Effect of anion secretion inhibitors on mucociliary transport in porcine tracheas. When anion secretion is inhibited with either the combination of bumetanide (Bum) and DMA or the anion channel blocker NPPB, mucociliary transport is greatly reduced compared to the control (C). Treatment with benzamil (Benz) to block ENaC-dependent liquid absorption preserves a significant fraction of mucociliary transport. Figure redrawn from Ballard *et al.* (2002).

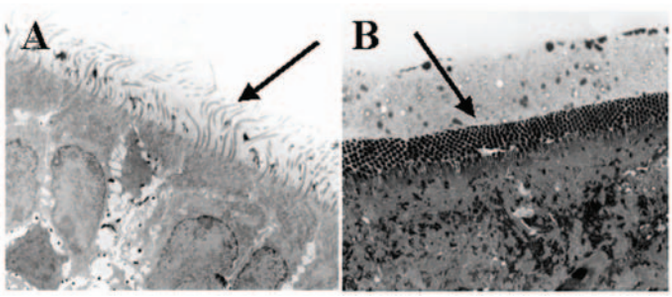



Figure 3. Effect of anion secretion inhibitors on airway cilia. A. Airway surface from control perfused pig lung. Cilia have normal appearance. B. Airway surface from perfused lung treated with bumetanide and DMA. Note that the cilia are collapsed between the thin, dense layer of mucus and the apical membrane of the epithelial cells. Figure taken from Trout *et al.* (2003).

to the depletion of airway surface liquid - a consequence of reduced liquid secretion in the face of ongoing liquid absorption.

These findings provide important insights into the aetiology of CF airway disease. If the secretion of liquid by the glandular airways is critically dependent upon CFTR, it is obvious that these same problems would occur in CF bronchi. Indeed, CF is characterized by mucin occlusion of submucosal glands, production of thickened mucus, and impaired mucociliary transport. One expects that inhaled bacteria, which become embedded in the airway surface mucus, would not be easily cleared because of the reduced mucociliary transport, predisposing the lungs to colonization. A possible caveat to this hypothesis, however, comes from a recent study suggesting that liquid secretion by submucosal glands is only partially disrupted in CF (Joo *et al.* 2002). A milder disruption in liquid secretion by glands might therefore take longer to manifest into the severe impairments of mucociliary transport that we see in the pig model and possibly explain why it may take several years for severe lung disease to develop in CF patients. Clearly, this issue will be the critical focus of future research efforts.

Stephen T. Ballard
*Department of Physiology, College of Medicine, University of South Alabama, USA*

## References

Ballard ST, Fountain JD, Inglis SK, Corboz MR & Taylor AE (1995). Chloride secretion across distal airway epithelium: relationship to submucosal gland distribution. *Am J Physiol* 268, L526-L531.

Ballard ST, Trout L, Bebök Z, Sorscher EJ & Crews A (1999). CFTR involvement in chloride, bicarbonate and liquid secretion by airway submucosal glands. *Am J Physiol* 277, L694-L699.

Ballard ST, Trout L, Mehta A & Inglis SK (2002). Liquid secretion inhibitors reduce mucociliary transport in glandular airways. *Am J Physiol* 283, L329-L335.

Inglis SK, Corboz MR,& Ballard ST (1998). Effect of anion secretion inhibitors on mucus content of airway submucosal glands. *Am J Physiol* 274, L762-L766.

Joo NS, Irokawa T, Wu JV, Robbins RC, Whyte RI & Wine JJ (2002). Absent secretion to vasoactive intestinal peptide in cystic fibrosis airway glands. *J Biol Chem* 277, 50710-50715.

Trout L, Corboz MR & Ballard ST (2001). Mechanism of substance P-induced liquid secretion across porcine bronchial epithelium. *Am J Physiol* 281, L639-L645.

Trout L, King M, Feng W, Inglis SK & Ballard ST (1998). Inhibition of airway liquid secretion and its effects on the physical properties of airway mucus. *Am J Physiol* 274, L258-L263.

Trout L, Townsley MI, Bowden A & Ballard ST (2003). Disruptive effects of anion secretion inhibitors on airway mucus morphology in isolated perfused pig lungs. *J Physiol* 549, 845-853.

### Rank Prize for Nutrition

Vadivel Ganapathy, member of the Editorial Board of *The Journal of Physiology*, has been awarded the Rank Prize for Nutrition in recognition of his work on the identification, molecular characterisation and control of cellular nutrient transporters. Vadivel is based at the Medical College of Georgia, USA and received his £20,000 from Lord Sainsbury of Turville at the Royal College of Physicians on 9 February.

### Back issues

The Publications Office has spare copies of some old volumes of *The Journal of Physiology* covering the period 1914 - 1940, although it may not be a complete set.

If anyone is interested in taking any of these issues, please contact Linda Rimmer (lrimmer@physoc.org)

### Archives

To complete the set of *Experimental Physiology* (formerly *The Quarterly Journal of Experimental Physiology*) and for archiving purposes, the Publications Office is looking for copies of volumes prior to 1998 (volumes 1 - 82).

If any reader has copies which they no longer need, please contact Emma Ward (eward@physoc.org). The Society could reimburse mailing costs if necessary.

# Gene expression profiling shows its muscle

With advances in genomic information and computational algorithms, the application of microarrays is uncovering new insights into muscle plasticity

Eric Stevenson (left) and Susan Kandarian

Our understanding of the mechanisms regulating skeletal muscle plasticity is still in its infancy. With the explosion of genomic information in the past decade, new tools have become available making it possible to obtain a global view of the changes in gene expression that underlie muscle adaptation. Transcriptional profiling has led to major advances in the understanding of biology in simple cellular systems. However, this degree of success has proven more elusive in complex tissues. It has become apparent, however, that with the proper focus and use of bioinformatics tools it is possible to design experiments that yield meaningful results. Several studies in recent years have successfully employed such techniques to develop a better understanding of the molecular processes that regulate muscle mass and plasticity.

Muscle atrophy is commonly thought of in terms of inactivity and sedentary life styles. However, profound muscle wasting also occurs with several pathological conditions. In these situations, muscle protein loss can become chronic and lead to severe complications and death. On the other hand, disuse atrophy is unique in that protein loss seems to reach an endpoint and actually involves an extensive process of remodelling. The mystery here is whether common or distinct pathways control atrophy in both situations. In an attempt to address this question, two groups have recently used expression profiling to identify common markers of atrophy in a variety of experimental models.

The majority of proteolysis during atrophy is mediated by the ubiquitin-proteasome system. Ubiquitin ligases (E3s) are involved in targeting specific proteins for degradation by the proteasome. Gomes and associates used microarrays to identify a previously uncharacterized gene that was highly induced in skeletal muscle during fasting (Gomes *et al.* 2001). Subsequent analysis showed that this gene was a novel muscle-specific E3 they named Atrogin-1 that is also induced with diabetes, cancer and renal failure. This same gene was concurrently cloned and characterized by another group and named muscle atrophy F-box (MAFbx) (Bodine *et al.* 2001). Differential display methods showed this gene was also induced in several models involving muscle disuse. In addition, they discovered another muscle-specific E3 activated in all disuse models, which they named muscle ring finger 1 (MuRF1). The finding that knockout mice lacking these genes are partially resistant to muscle atrophy following denervation is a testament to their functionality as universal mediators of atrophy.

By analyzing gene expression at multiple time points, clustering algorithms can be used to identify sets of coordinately regulated genes. Early work with yeast demonstrated the power of this approach in identifying regulatory networks. Since muscle adaptations likely involve the coordinated actions of many genes working in parallel, the potential use for such methods to study muscle biology becomes obvious. Several studies have emerged that have shown that these methods can also be adapted to studying regulatory mechanisms even in a tissue as complex as skeletal muscle.

Our laboratory has used this approach to analyze how gene expression patterns change at multiple time points during the first 14 days of disuse atrophy in rats (Stevenson *et al.* 2003). This analysis provided us with an abundance of new genes to study, including another E3, Nedd4, that is activated during atrophy. However, it was the temporal aspect to the study that provided us with even more information. Clustering was used to segregate differentially expressed genes into sets sharing similar activation or deactivation patterns during atrophy. This allowed the development of a timeline with respect to behaviour of genes in a broad array of functional categories. One of the most interesting elements involved the fact that regulatory genes, while often upregulated early, were also in clusters that represented genes with distinct peaks during the later stages of atrophy. This supports the idea that the atrophy process is marked by several sequential phases. For example, genes that are activated in early clusters may activate the genes involved in protein degradation, but the maintenance of this phenotype may be regulated by genes that fall into clusters representing later activation.

Other groups have taken this approach a step further by using temporal expression patterns to identify downstream targets of MyoD. It is well established that MyoD is an arbiter of myogenic lineage, but it has also been shown to modulate the transcriptional response of muscle genes to different activity paradigms. Indeed, MyoD expression is activated during muscle regeneration, and with increased or decreased mechanical loading. In each of these situations, MyoD activates or deactivates a small subset of the genes that contain MyoD binding sites in their promoters. Therefore, the question arises as to how such specificity is accomplished in each of these situations.

Bergstrom *et al*. (2002) have used temporal expression profiling to investigate how MyoD orchestrates the process of differentiation. MyoD overexpression was used to induce

differentiation in MyoD$^{-/-}$/Myf5$^{-/-}$ fibroblasts, and expression was measured at several time points using microarrays. By using cyclohexamide to inhibit synthesis of other activated regulatory factors the authors were able to strictly identify targets of MyoD. Using clustering they were able to show that MyoD can initiate several distinct subprograms of gene expression through promoter-specific recognition rather than global activation of all MyoD regulated genes.

Another group was able to use similar techniques *in vivo* to discover novel targets of MyoD activated during muscle regeneration (Zhao *et al.* 2002). As expected, MyoD and several of its known downstream targets were activated at a time point consistent with the formation of new fibres. Clustering was used to identify genes with an activation pattern similar to that of Ulip, one of these known targets.

Promoter databases and sequence analysis tools were then used to show that a small subset of these genes actually had potential MyoD binding sites in their promoters. Gel-shift assays and chromatin immunoprecipitation were used to discover a functional binding site in the promoter of Slug, a member of the snail/slug family of transcriptional repressors. The functionality of this relationship was demonstrated *in vivo* using slug-dependent reporter constructs and through the demonstration that Slug-null mice show impaired ability to regenerate after injury.

As the studies described herein show, a good deal of progress has been made in the development of effective microarray studies in muscle. With the development of increasingly sophisticated annotation and analysis tools and the introduction of whole-genome chips, this area of research promises to be as much as a boon to the field of muscle biology as it has to other less complex systems cellular systems.

Eric J Stevenson
Susan C Kandarian
*Boston University, Boston, MA, USA*

## References

Bergstrom DA, Penn BH, Strand A, Perry RL, Rudnicki MA & TapscottSJ (2002). Promoter-specific regulation of MyoD binding and signal transduction cooperate to pattern gene expression. *Mol Cell* 9, 587-600.

Bodine SC, Latres E, Baumhueter S, Lai VK, Nunez L,Clarke BA, Poueymirou WT, Panaro FJ, Na E, Dharmarajan K, Pan ZQ, Valenzuela DM, DeChiara TM, Stitt TN, Yancopoulos GD & Glass DJ (2001). Identification of ubiquitin ligases required for skeletal muscle atrophy. *Science* 294, 1704-1708.

Gomes MD, Lecker SH, Jagoe RT, Navon A & Goldberg AL (2001). Atrogin-1, a muscle-specific F-box protein highly expressed during muscle atrophy. *Proc Natl Acad Sci U S A* 98, 14440-14445.

Stevenson EJ, Giresi PG, Koncarevic A & Kandarian SC (2003). Global analysis of gene expression patterns during disuse atrophy in rat skeletal muscle. *J Physiol* 551, 33-48.

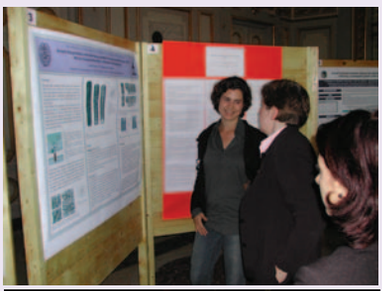
Zhao P, Iezzi S, Carver E, Dressman D, Gridley T, Sartorelli V & Hoffman EP (2002). Slug is a novel downstream target of MyoD. Temporal profiling in muscle regeneration. *J Biol Chem* 277, 30091-30101.

## New International Secretary

David Eisner (left) was appointed at the Extraordinary General Meeting of the Society in Cambridge in December to take over as International Secretary from David Brown. David Eisner is based in the Unit of Cardiac Physiology at Manchester. He was a member of the Editorial Board of *The Journal of Physiology* from 1991 - 2000, during which time he served as a Distributing Editor (1993-1994), Press Secretary (1994-1997) and Chairman (1997-2000), and has been a Member of the Society since 1980.

## Neuroscience Workshop

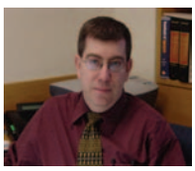
Bucharest, Romania was the venue for the recent Physiological Society Workshop held from 23 - 25 September, 2003 (pictures below). See *Physiology News* 2003, **53**, 40 for a full report



Above: Speakers and students take a break on the steps of the Carol Davilla University
Right (top): Magdalena Budisteanu and Maihri Macrae discuss a poster
Right (bottom): Ana-Maria Zagrean – organiser extraordinaire

# Control of upper airway muscles and the pathophysiology of obstructive sleep apnoea

OSA is more than just a loud case of snoring - it hs been described as 'the most important new disease discovered in the second half of the 20th century'. But why do airways close during sleep but not when we are awake? Robert Fogel offers an explanation



Robert Fogel

Obstructive sleep apnoea (OSA) is a common disorder, affecting approximately 2% to 4% of middle-aged women and men in the United States (Young *et al.* 1993). This disorder is characterised by recurrent sleep-induced collapse of the pharyngeal airway, leading to hypoxaemia and hypercapnia (elevated blood $CO_2$ levels), with arousal from sleep being required to re-establish airway patency. While the pathophysiology of this disorder is complex, and incompletely understood, most evidence supports the concept that patients with OSA have an anatomical predisposition to airway collapse (Schwab *et al.* 1995). However, during wakefulness protective mechanisms maintain pharyngeal airway patency by increasing the activity of pharyngeal dilator muscles. These protective mechanisms fail during sleep, with subsequent collapse of the pharyngeal airway behind the palate, tongue or both. Thus understanding the mechanisms controlling the human upper airway muscles is paramount to understanding the disorder. This article reviews some of the recent data regarding control of upper airway muscles in humans during wakefulness and sleep, as it applies to the pathogenesis of OSA.

The pharyngeal airway is a complex structure whose functions include respiration, speech, and swallowing. It is hypothesised that the evolution of speech in man, which requires substantial mobility of the larynx, led to the loss of rigid support of the hyoid bone which is present in most mammals. The human pharyngeal airway is thus largely dependent on muscle activity to maintain patency.

The muscles of primary importance fall into three groups:

(i) the muscles influencing hyoid bone position;
(ii) the muscle of the tongue (genioglossus); and
(iii) the muscles of the palate.

The activity of many of these muscles is increased during inspiration, and this acts to counterbalance the collapsing influence of negative airway pressure. These muscles are referred to as inspiratory phasic upper airway muscles with the genioglossus being the best studied. Other muscles such as the tensor palatini do not demonstrate inspiratory phasic activity, but instead maintain a relatively constant level of activity. These are called tonic, or postural muscles and are also thought to play a role in the maintenance of airway patency. These two types of pharyngeal muscles are likely controlled by groups of neurones within the brainstem that have different firing patterns relative to the respiratory cycle and may behave quite differently during wakefulness and sleep.

It is known that the activity of the genioglossus is carefully controlled by a number of variables (Fig. 1) including:

(i) central pattern generating neuron output from the ventrolateral medulla;
(ii) respiratory chemostimulation via rising $pCO_2$ or falling $pO_2$;
(iii) a 'wakefulness drive' that may work through state-dependent systems outlined below.

Finally, it appears that negative pressure in the pharynx is the most important local stimulus to genioglossal muscle activation on a moment by moment basis. Either a rapid pulse of negative pressure applied to the pharyngeal airway, or the application of inspiratory resistive load leads to an immediate and robust activation of this muscle in humans, and the increase in genioglossus muscle EMG (GGEMG) is proportional to the size of the load (Horner, 1991; Malhotra *et al.* 2000). In addition, if humans are ventilated using an iron-lung (negative pressure ventilator), when central pattern generating input can be largely abolished (as measured by an absence of phasic diaphragm EMG), there remains a linear relationship between pharyngeal negative pressure and genioglossal EMG (Fogel *et al.* 2001). This relationship remains constant over a range of negative pressures and is not affected by alterations in $CO_2$ levels. This system thus provides a mechanism by which the pharyngeal muscles can respond on a moment by moment basis to changes in local pharyngeal conditions.

In the patient with OSA, in the face of a smaller and more collapsible upper

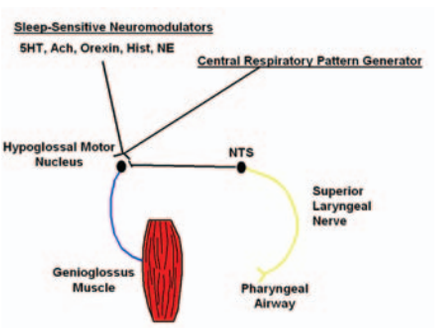



Figure 1. Neuromuscular inputs controlling genioglossal muscle activity. Genioglossal muscle activation is controlled by a variety of inputs as illustrated in this figure. The hypoglossal motor nucleus receives direct input from central pattern generating neurons in the brainstem that control phrenic nerve activity (upper right of figure). In addition, afferent signals (which appear to detect negative pressure) are transmitted from the pharyngeal airway via the superior laryngeal nerve (yellow line) synapsing initially in the nucleus of the solitary tract (NTS) and then providing feedback to the hypoglossal nerve. Finally, multiple excitatory state dependent neurotransmitter systems (such as serotonin [5HT], norepinehrine [NE], acetylcholine [Ach], orexin and histamine [hist]) all project monosynaptically to this motor nucleus. The activity of each of these systems diminishes during sleep.

airway, genioglossal and tensor palatini muscle activity have been demonstrated to be higher during wakefulness than in healthy individuals, probably secondary to the reflex mechanisms outlined above. The application of nasal continuous positive airway pressure (which decreases negative pressure fluctuations in the pharynx), decreases GGEMG to a much greater extent in apnoea patients, suggesting augmented activation of this negative pressure reflex in these patients. In addition, the tonic (expiratory) GGEMG is higher in the apnoea patient than in controls. While increased negative pressure is likely driving the increased phasic activity of the genioglossus, what controls tonic activation of this muscle is poorly understood.

The effects of sleep on pharyngeal muscle function are quite profound as well. In normal individuals, GGEMG falls slightly at sleep onset, but then recovers to near waking levels in the face of increased pharyngeal resistance. When placed on nasal continuous positive airway pressure, the initial sleep-induced decrease in GGEMG is not altered, suggesting that this initial fall is due solely to the removal of a 'wakefulness' drive in normal individuals.

Sleep is also a state that is associated with a significant reduction in multiple neural reflex mechanisms, including postural, spindle-driven reflexes. This appears to be the case for negative pressure reflexes in the upper airway as well. Studies suggest that during non-rapid eye movement (non-REM) sleep this negative pressure reflex is substantially diminished (Wheatley *et al.* 1993). Furthermore, the relationship between changes in epiglottic pressure and GGEMG is much lower during sleep. During passive negative pressure ventilation in the iron-lung, there is a marked reduction in the GGEMG response to negative pressure during non-REM sleep compared to wakefulness, leading to a rise in airflow resistance, and in some normal subjects the development of airway obstruction (Fig. 2) (Fogel *et al.* 2003). The state-dependent neural mechanisms

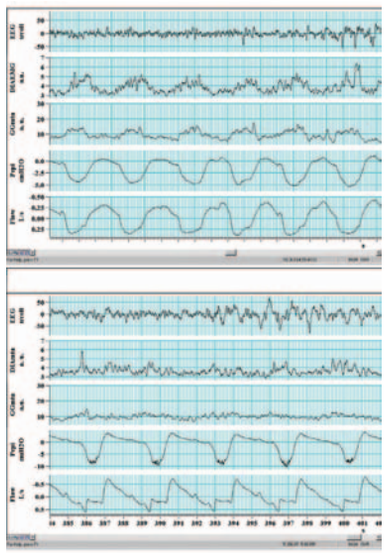


Figure 2. Loss of phasic GGEMG during negative pressure ventilation during stable non-REM sleep. Raw data from one individual shows that during stable non-REM sleep during basal breathing, phasic GGEMG activity is still seen. However, during Negative Pressure Ventilation, phasic GGEMG is largely absent, despite more negative intrapharyngeal pressure, and is associated with the development of inspiratory airflow limitation (bottom).

responsible for the loss of these neural reflex mechanisms is unclear at this time. However, virtually all neurotransmitter systems driving wakefulness (serotonin, noradrenaline, acetylcholine, histamine and orexin) project monosynaptically to the hypoglossal motor nucleus (controlling the genioglossus) and all are excitatory. Thus, when these neural systems become less active during sleep, it is not surprising that muscle activity falls.


From the data reviewed above, it would seem that the primary defect in obstructive sleep apnoea is an anatomically small or collapsible pharyngeal airway. During wakefulness, neuromuscular compensatory systems function to increase the activity of the pharyngeal dilator muscles, thus preserving airway patency.

However, this reflex-driven augmented muscle activity is lost at sleep onset, and collapse of the pharyngeal airway occurs. The associated hypoxaemia and hypercapnia drive increase respiratory effort and, ultimately, arousal from sleep occurs, thus re-establishing airway patency and ventilation. Once the patient returns to sleep, the cycle begins again. The patient thus suffers the consequences of repeated sleep disruption as well as recurrent hypoxaemia and hypercapnia.

As we learn more about the basic neural pathways that control upper airway muscle activity during wakefulness and sleep, the hope is that more specific therapy for this important disorder can be developed.

Robert B. Fogel
*Instructor in Medicine, Harvard Medical School & Associate Physician, Division of Sleep Medicine, Brigham and Women's Hospital, Boston, MA, USA*

## References

Fogel R, Malhotra A, Pillar G, Edwards J, Beauregard J, Shea S & White D (2001). Genioglossal activation in patients with obstructive sleep apnea versus control subjects. Mechanisms of muscle control. *Am . Resp Cri. Care Med* 164, 2025-2030.

Fogel RB, Trinder J, Malhotra A, Stanchina M, Edwards JK, Schory KE & White DP (2003). Within-breath control of genioglossal muscle activation in humans: effect of sleep-wake state. *J Physiol* 550, 899-910.

Horner RL, Innes, JA, Murphy K & Guz A (1991). Evidence for reflex upper airway dilator muscle activation by sudden negative airway pressure in man. *J Physiol* 436, 15-29.

Malhotra A, Pillar G, Fogel R, Beauregard J & White D (2000). Genioglossal but not palatal muscle activity relates closely to pharyngeal pressure. *Am J Resp Crit Care Med* 162, 1058-1062.

Schwab RJ, Gupta KB, Gefter WB, Metzger LJ, Hoffman EA & Pack AI (1995). Upper airway and soft tissue anatomy in normal subjects and patients with sleep-disordered breathing. Significance of the lateral pharyngeal walls. *Am J Resp Crit Care Med* 152, 1673-1689.

Wheatley J, Mezzanotte W, Tangel D & White D (1993). Influence of sleep on genioglossus muscle activation by negative pressure in normal men. *Am Rev Respir Dis* 148, 597-605.

YoungT, Palta M, Dempsey J, Skatrud J, Weber S & Badr S (1993). The occurrence of sleep-disordered breathing among middle-aged adults. *New Engl J Med* 32, 1230-1235.

# Saving British science

Save British Science is approaching its 20th anniversary as a leading science lobby group. Joe Lamb, founding Chairman of SBS and recently retired from its Executive Committee, explains the Physiological Society's crucial role in its establishment

Joe Lamb, Committee Secretary of the Physiological Society from 1982-1985 and founder of the *Committee Newsletter* - forerunner of the *Magazine* and *Physiology News* (see also p. 30 in this issue)

In 1982, when I was Committee Secretary of the Physiological Society, it became apparent to me that the then government, run by Mrs Thatcher, was not interested in scientific research. It was also apparent that scientists were more likely to impress the government if they spoke with one voice, rather than disparate voices calling for more support for chemistry, physics and so on.

The Committee later agreed to form a new organisation which we called 'An Association of Learned Societies in Science'. I wrote to all the societies we could identify proposing such an organisation and suggesting that each society send two representatives - their secretary and one other.

We had a number of meetings with representatives from most of the major scientific societies in the UK, discussing our lack of funding and trying to decide how best to proceed, for we had little expertise in influencing government. We had no money to employ a lobbying organisation and, in any case, Tam Dalyell advised me that it would be better to organise the campaigning ourselves. So I wrote to Keith Joseph, then Secretary of State for Education and Science, to discuss our concerns, only to find he was not willing to meet us.

Eventually the problem of attracting the attention of those in power was solved for us when Mrs Thatcher declared that academics were poor because they were pricing themselves out of jobs with large pay rises. We all felt this was nonsense but had no data to support our view. I therefore contacted Jon Turney, then at the Science Policy Research Unit at Sussex (SPRU), who very helpfully prepared a report on science funding for us. I also collected all the published data for research council incomes and the dual support element of the University Grant Commission grant, to which I applied the sophistication factor suggested by the Science and Engineering Research Council. Both of these sources suggested that basic science funding was declining, with an estimated deficit of 19% for 1984/1985 compared to 1977/1978. I then thought we should collect data 'at the coalface' and, having failed to find a proper statistician to do the work, I applied to the SSRC for a small grant to do it myself. This grant of £500 enabled me to visit a variety of departments of different disciplines in Edinburgh, Dundee, Glasgow and St Andrews to collect data on equipment and running costs.

The results (*New Scientist* **107**, 61) showed that salaries were rising with inflation but that capital and recurrent costs were increasing at between 2% and 7% above the rate of inflation. The pressure on our budgets was thus due to external factors, not to pay costs. This was, I think, the first time that it was shown that the Retail Price Index (RPI) was not a good judge of the costs of doing science. A few years later Yale University showed that such costs inflated at 2% above the US RPI. Despite this evidence, successive UK governments in the 1980s and early 1990s kept decreasing research budgets, both for universities and for government departments, a situation not reversed until New Labour came to power in 1997. The underfunding in the 80s and early 90s was all the more extraordinary in that the UK was enjoying large revenues from North Sea oil, an industry based on the application of basic science.

During this time I was surprised to get a letter from an administrator at the Royal Society saying that our name was inappropriate as we did not represent all scientific societies. Although this attitude seemed unreasonable to me, especially as the Royal Society was apparently making no effort to lobby the government on research funding, I did not think it helpful to show scientists quarrelling and so changed our name to the Ad-hoc Group on Research Funding (AGREF). I learned later that the social scientists had beaten us to it by forming a group called An Association of Learned Societies in the Social Sciences, which still exists, although I am unsure if it represents all the social sciences.

In 1985 Denis Noble rang me to ask to look at the figures I had collected to prepare him for seconding the Oxford debate about the proposed honorary degree for Mrs Thatcher. I sent these on and had a letter from him saying how essential they had been. Because of this I was asked to a meeting in Oxford in the autumn of 1985 to discuss a further campaign on research funding. My recollection was that this meeting was largely organised by the physicists - but took place in Balliol, Denis Noble's College. The idea floated was for a half page advert in *The Times* stating our case for more funding. I regret that I was doubtful of the value of this approach, a view which turned out to be totally wrong. We made up the advert and set up the mechanism for collecting the necessary £6000. We also spent much time on an appropriate name for the new organisation. I seem to remember I suggested Save Our Science (SOS) which was fortunately changed to Save British Science by Denis Noble.

The Oxford connection was vital. There were so many contacts between Oxford

and the media that when, on the 13 January, 1986, the advert appeared in a good position in *The Times*, it was accompanied by a letter and an appearance on the Today programme (badly done by me, partly due to inexperience). Another advantage was that our first office was sited in Nuclear Physics at Oxford; as so many media people were from Oxford this meant that they were always ready to pop down for a meeting. The only problem was that Michael Heseltine resigned at the same time, which deflected some attention from us. As SBS was clearly going to have a much higher profile than AGREF, I closed down AGREF. Another vital decision made then was to appoint John Mulvey as the first secretary of SBS, a post he occupied with great distinction for many years. I was surprised to be asked to be the first chairman and served for 10 years.

I soon saw the value of the public advert in *The Times* when Keith Joseph phoned me and demanded a meeting - a welcome change from before. At the meeting he expressed surprise that we felt hard up for 'no-one had told him so'; he asked us for suggestions as to how he was to distribute the available research money (we said this was not our job and so refused to do so); he would not accept the evidence from other countries that research was an economic good ('foreigners are different'). He ended by saying it had been a useful meeting and asked if we would come to see him every month. We wanted to preserve our independence, so felt this was inadvisable and declined.

In retrospect I realise that Keith Joseph and his advisers did not appreciate the difference between tacit and codified knowledge. The point we tried to make then, and since, is that, although knowledge is published and available to all as a 'public good', it cannot be used unless the users have the tacit knowledge in their heads to do so. This requires much training of the users, which means that a country must invest in first class educational and research facilities. Our view about the economic good arising from basic research, although not at the time based on much economic knowledge, was subsequently confirmed by Robert Solow of MIT who won the Nobel Prize in 1987 for his work over many decades showing that US wealth depended on publicly funded basic science.

We planned that the executive members of SBS would be drawn from university and government labs and also from industries which depended on a good basic science base. In the event we were disappointed that no-one from industry would join us as we were regarded as 'not one of us'; indeed one of the speakers I asked to give our annual lecture said that he could only do so as he was working in the City at the time, and not in industry.

As time passed people came to understand that we were not against the government but simply against the very poor support that basic science was getting. Things improved when John Major appointed William (now Lord) Waldegrave as Minister for Science, the first for some 30 years. On assuming office, Waldegrave asked firstly the then President of the Royal Society and secondly SBS to meet him. John Mulvey and I developed a close relationship with Waldegrave and with his chief scientist Bill Stewart. Things became more difficult when Michael Heseltine, as Deputy Prime Minister, abruptly moved the office of the Science Minister out of the Cabinet Office and into the Department of Trade and Industry. Eventually basic science funding started to show a real increase with the election of the Blair government in 1997. By this time, various parts of industry and many scientific societies were funding SBS, so that today we can afford to keep our excellent Director, Peter Cotgreave, his PA, Susan O'Dwyer, and two researchers, Alice Sharp Pierson and Rosemary Davies, in an office in UCL.

SBS has become the first port of call for journalists who want a view on science policy issues and might even be a model for scientists in other countries who wish to campaign about scientific policy matters. We have established this position because we have had Directors who were excellent scientists but chose to take on the SBS job and so could speak with authority on matters scientific. In addition, they were almost always at the end of a telephone to give instant answers to the media and they and other members were always willing to give talks and write articles and letters on most aspects of science policy. The Newsletter, under its editor Peter Saunders, has become a valuable means of communicating with a much wider audience. A rather curious feature is that several longer established organisations sometimes find it convenient to filter their views through us in circumstances when making a direct statement would pose political problems for them.

When starting out on this venture 20 years ago I never imagined that one day my successor would be discussing with the Prime Minister of the day (Tony Blair) whether it was nearing the time for us to be disbanded as Science was Saved, or at least to change our name to Supporting British Science. However, I am afraid that time has not yet arrived.

Joe Lamb
*Emeritus Professor of Physiology, University of St Andrews, Fife*

## Physiologists in the news ...

Two big stories relating to physiology have featured widely in the national print and broadcast media in the last couple of months. The first was the Honours List furore and the reported omission of Colin Blakemore's name. This story and its sequelae continue to gather column inches, mostly concerning the Government's attitude to science and scientists. The question of how far the Government backs scientists who publicly engage in debate on scientific issues, particularly animal experimentation, has been the focus of many stories.

The second story was the decision of Cambridge University not to go ahead with the Primate Neuroscience Centre (see *Physiology News* 50 and 51), which broke just a few days before this issue went to press. The Society has issued a statement via its website expressing its 'deep disappointment' at the decision. We hope to discuss both stories in more detail in the next issue.

Austin Elliott

# Twenty years of Society magazines

The Physiological Society *Committee Newsletter* - forerunner of the *Newsletter*, the *Magazine* and, most recently, *Physiology News* - was conceived in 1983 by the then Committee Secretary Joe Lamb. Past Editors look back on their time in the hot seat








From the top: Joe Lamb, founder of the Newsletter (top left), Past Editors John Stephens (top right), Tony Short, Alison Brading, Kwabena Appenteng, Saffron Whitehead and Bill Winlow. The present Editor, Austin Elliott, is pictured above

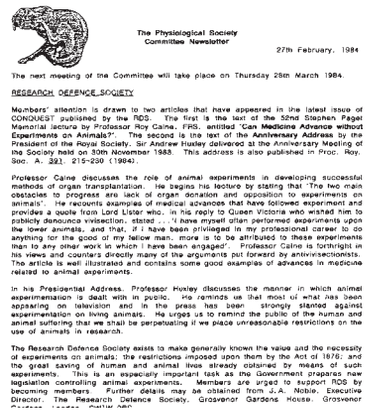
## The origin of the Newsletter

I became Committee Secretary in 1982, without having first been Meetings Secretary, for Charles Michel wished to stop after running the Society's meetings. Once I settled in I realised that, although the Society ran very good, well attended meetings and published excellent journals, other societies were leaving us behind with certain 'housekeeping' functions. This arose, I think, largely because the Committee Office was moved every 3 years to a new location, so there was little continuity. I looked at how other societies operated and suggested that we start a Newsletter for general news items and to increase communication between Members and the Executive; arranged for Heads of Departments to meet to discuss their common problems; and approached the Wellcome Trust to fund a lecture for young physiologists, ideally those in less fashionable departments. We also, uniquely, started an organisation to lobby the Government on the low level of funding for basic science (see p. 28). After some discussion the Committee agreed to these changes and so the Newsletter was born, initially as cyclostyled sheets edited by John Stephens, but eventually it grew into its present healthy form.

Joe Lamb

## 1983 – 1984

Known for my after-dinner speaking at Society Meetings, and as a member of the younger generation on the Committee, I was asked by the then Honorary Secretary to put together a newsletter. This was intended to improve the poor communication that existed between the Committee and Ordinary Members of the Society. But so concerned were members of the Committee about what I might say, that they decided they should vet the


The Physiological Society
Committee Newsletter

27th February, 1984

The next meeting of the Committee will take place on Thursday 26th March 1984.

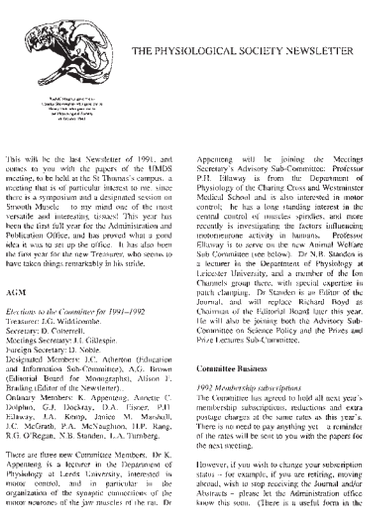
RESEARCH DEFENCE SOCIETY

Members' attention is drawn to two articles that have appeared in the latest issue of CONQUEST published by the RDS. The first is the text of the 52nd Stephen Paget Memorial lecture by Professor Roy Calne, FRS, entitled 'Can Medicine Advance without Experiments on Animals?'. The second is the text of the Anniversary Address by the President of the Royal Society, Sir Andrew Huxley delivered at the Anniversary Meeting of the Society held on 30th November 1983. This address is also published in Proc. Roy. Soc. A. 391, 215-230 (1984).

Professor Calne discusses the role of animal experiments in developing successful methods of organ transplantation. He begins his lecture by stating that 'The two main obstacles to progress are lack of organ donation and opposition to experiments on animals'. He recounts examples of medical advances that have followed experiment and provides a quote from Lord Lister who, in his reply to Queen Victoria who wished him to publicly denounce vivisection, stated '...I have myself often performed experiments upon the lower animals, and that, if I have been privileged in my professional career to do anything for the good of my fellow man, more is to be attributed to these experiments than to any other work in which I have been engaged'. Professor Calne is forthright in his views and counters directly many of the arguments put forward by antivivisectionists. The article is well illustrated and contains some good examples of advances in medicine related to animal experiments.

In his Presidential Address, Professor Huxley discusses the manner in which animal experimentation is dealt with in public. He reminds us that most of what has been appearing on television and in the press has been strongly slanted against experimentation on living animals. He urges us to remind the public of the human and animal suffering that we shall be perpetuating if we place unreasonable restrictions on the use of animals in research.

The Research Defence Society exists to make generally known the value and the necessity of experiments on animals; the restrictions imposed upon them by the Act of 1876; and the great saving of human and animal lives already obtained by means of such experiments. This is an especially important task as the Government prepares new legislation controlling animal experiments. Members are urged to support RDS by becoming members. Further details may be obtained from A.A. Noble, Executive Director, The Research Defence Society, Grosvenor Gardens House, Grosvenor


THE PHYSIOLOGICAL SOCIETY NEWSLETTER

This will be the last Newsletter of 1991, and comes to you with the papers of the UMDS meeting, to be held at the St Thomas's campus, a meeting that is of particular interest to me, since there is a symposium and a designated session on Smooth Muscle - to my mind one of the most versatile and interesting tissues! This year has been the first full year for the Administration and Publication Office, and has proved what a good idea it was to set up the office. It has also been the first year for the new Treasurer, who seems to have taken things remarkably in his stride.

AGM

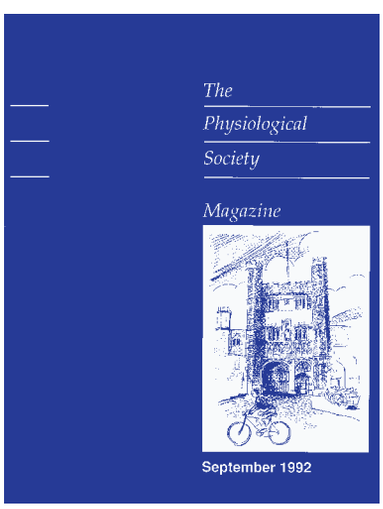
*Elections to the Committee for 1991–1992*
Treasurer: J.G. Widdicombe
Secretary: D. Colverell.
Meetings Secretary: J.I. Gillespie.
Foreign Secretary: D. Noble.
Designated Members: J.C. Atherton (Education and Information Sub-Committee), A.G. Brown (Editorial Board for Monographs), Alison T. Brading (Editor of the Newsletter).
Ordinary Members: K. Appenteng, Annette C. Dolphin, G.J. Dockray, D.A. Eisner, P.H. Ellaway, J.A. Kemp, Janice M. Marshall, J.C. McGrath, P.A. McNaughton, H.P. Rang, R.G. O'Regan, N.B. Standen, L.A. Turnberg.

There are three new Committee Members. Dr K. Appenteng is a lecturer in the Department of Physiology at Leeds University, interested in motor control, and in particular in the organization of the synaptic connections of the motor neurones of the jaw muscles of the rat. Dr Appenteng will be joining the Meetings Secretary's Advisory Sub-Committee. Professor P.H. Ellaway is from the Department of Physiology of the Charing Cross and Westminster Medical School and is also interested in motor control; he has a long standing interest in the central control of muscles spindles, and more recently is investigating the factors influencing testosterone activity in humans. Professor Ellaway is to serve on the new Animal Welfare Sub Committee (see below). Dr N.B. Standen is a lecturer in the Department of Physiology at Leicester University, and a member of the Ion Channels group there, with special expertise in patch clamping. Dr Standen to go Editor of the Journal, and will replace Richard Boyd as Chairman of the Editorial Board later this year. He will also be joining both the Advisory Sub-Committee on Science Policy and the Prizes and Prize Lectures Sub-Committee.

Committee Business

*1992 Membership subscriptions*
The Committee has agreed to hold all next year's membership subscriptions, reductions and extra postage charges at the same rates as this year's. There is no need to pay anything yet - a reminder of the rates will be sent to you with the papers for the next meeting.

However, if you wish to change your subscription status – for example, if you are retiring, moving abroad, wish to stop receiving the Journal and/or Abstracts – please let the Administration office know this soon. (There is a useful form in the




*The Physiological Society Committee Newsletter*, first published in 1983 (top). *The Physiological Society Newsletter* (middle), was published in this form from November 1984 until September 1992, when it was relaunched as*The Physiological Society Magazine* (above)



The Millenium saw a relaunch of *The Physiological Society Magazine* (top), followed in 2001 by the present *Physiology News* (above)

contents. Joe (open government) Lamb was less sure. Vetting was abandoned after the first issue, which appeared in May 1983.

It was produced using the latest in dedicated word processors (thanks A Taylor) and assembled using double-sided tape. The first item was subscriptions. They were going up. The second described how Anne Warner had made a convincing case to the Committee for the Society to set up an Advanced Cell Physiology Course at Plymouth. The third discussed the format of Meetings (again).

But the most important item was two sentences about the impending publication of a Home Office Green Paper framing new legislation controlling the use of animals in research and teaching (*gratiae opera tua*, Cec Kidd). This issue soon came to dominate the affairs of the Society and its Officers. In tune with the times I selected a picture of the Society Dog to be the logo of the newsletter.

John Stephens

## 1984 - 1988

My recollection of the Committee newsletters are of their being very slight affairs, designed originally to summarise Committee discussions for the membership as a whole rather than the minority who attended the Annual General Meeting. They gave no hint of what their successor, the magazine, would become.

Tony Short

## 1989 – 1992

At the time of my election to the Physiological Society Committee in 1988, it was customary for one of the newly appointed members to take on the editorship of the Society's *Newsletter*, and I was persuaded to take over from Tony Short (then a lecturer in the Physiology and Pharmacology Department of the University of Nottingham Medical School) who had served his term.

At that time this was very much a 'one man show'. It was up to the Editor to compose, type and produce the *Newsletter*, usually twice a year, and get sufficient copies made for distribution with the Meeting papers to Members of the Society. In those days there were still nine meetings a year, and the tradition that there were always Society Meetings at University College (London), Oxford and Cambridge was just being revised, with each department agreeing to give up one Meeting in five to allow them to be held in more departments. The idea for the newsletter was to get one out before the AGM, and one at a later Meeting to report any outcomes from the AGM.

I was responsible for at least six issues, the last being in October 1991. I learnt a lot during that time about producing material for publication. I used a Macintosh computer, but there was little specialized software available at that time. I was fortunate in having a colleague with a much greater knowledge of desk-top publishing and a very sharp eye, who was willing to criticise (vigorously) my efforts. I learnt about layout, columns, fonts, em and en spaces and dashes, small caps and sundry other things, and had my punctuation corrected. The look of the *Newsletter* improved, and it grew somewhat in size, the last issue being six pages long! During 1991 the Society set up an Administration and Publications Office in Oxford, and in 1992 Kwabena Appentang (then Lecturer in the Department of Physiology at Leeds University) became Editor of the *Newsletter*, and the Office took over its production. *(We have been unable to contact Kwabena for a comment. Ed)*

There is no doubt but that the Newsletter in my day was somewhat boring, and only a poor forerunner of the elegant *Physiology News* of today. The main problem was that, apart from Committee and Society business, Editors relied on Members to provide the material for the newsletter, and it was a constant disappointment to me how few actually contributed anything. I tried to encourage cartoons, but only elicited one from Heather Dalitz - key member of the Office staff at that time – showing the then Treasurer, Julian Jack, gloating over the Society's monetary assets on one side and dreaming about neurones on the other side of a frantically working administrative officer. Tilli Tansey from the Wellcome Institute contributed some interesting 'Traces of the Past', and I started a column for people looking for a good home for their old journals. Apart from that, it was a useful medium for keeping members abreast of what was happening in the society, but otherwise, I have to admit - dull.

Alison Brading

## 1994 – 1998

It all started at a Physiological Society dinner (at the Royal Free to be precise) where I was sitting on a table with Kwabena (then Editor). With glass of wine in hand, he started talking about

*The Physiological Society Magazine* and I started retaliating about my hobby as a freelance journalist. I like to blame the excess of good wine for my ability to show off as I did.

The upshot of my indiscretions was that Kwabena asked me to write and commission some articles about Science and The Media. These were printed in the April and June issues in 1993. The next step followed - Richard Boyd phoned out of the blue to ask if I would like to become Editor of *The Physiological Society Magazine*. Flattery – yes: caution – sleep on it: but I knew I would say yes. I accepted the next day and (I regret) without approval of my then Head of Department. So that's how I ended up as Editor.

The central office of the Society was then in Oxford and I was duly invited up to learn the ropes. For a while the *Magazine* production was shuffled between Oxford and London, where I am based, but finally the whole production of the *Magazine* was transferred to St George's Hospital Medical School. At that time John Widdicombe (retired Head of my Department) was Treasurer of the Physiological Society and his offices were also at St George's. The treasury office, that provided me with tremendous support in the early days, and the *Magazine* office became a happy enclave of the Society.

There was lots of fun being Editor. I became a member of the then Physoc Committee with Committee dinners, meetings, foreign travel and friendship. But this was icing on the cake between commissioning, editing, proof reading and overseeing the production. There were many days and nights when panic would set in. Why do contributors fail to reach deadlines? What image are we going to put on the front cover? In terms of the lay-out, how are we going to fill up this page? What should be the title and leader to each article? Using QUARK, Denise Redmond in the AVA Department at St George's produced all the *Magazine* layout and finally the tiny disc would be sent to the printers. A week or so later the proofs would arrive – yet more spelling mistakes discovered and, horrors, the wrong caption was under the wrong photograph. Any changes at this stage meant increased costs of production, so how much would each correction actually cost? More decisions to be made about essential corrections and the concern about the costs to the Society. I could await the angry emails from contributors. The final worry was whether or not the printers would deliver in time for dispatch to Oxford and distribution to Members of the Society. More stress and the next edition was already being commissioned.

During my time as Editor, the *Magazine* production was cut from six issues a year to four seasonal issues. This eased some of the pressure but I was still trying to keep up my teaching and research commitments. The latter took its toll. But I have no regrets because I learnt a lot, I made friends and most of all it was a challenge. Since I retired gracefully, the *Magazine* has changed considerably, but it looks great these days.

It can't all have been bad because I have returned for more punishment. I am currently Editor of the British Endocrine Society newsletter - this time in name rather than being in charge of the complete production. As Robert Southwell said (16th century) 'Times go by turns, and chances change by choice'. I took the time and the chances and the *Magazine* was part of my changing life.

Saffron Whitehead

## 1999 – 2003

Before putting pen to paper, I read all the comments from previous Editors and it's interesting to see different people's perceptions of how the magazine has developed over the past 20 years.

I can probably thank (blame?) Saffron Whitehead for convincing me of what a good idea it would be to become Editor of the magazine. She mentioned all the plusses, including being a member of the Physiological Society Committee, but not all the headaches.

On taking on the job, I had support from Craigie Chappas as editorial assistant in the London Office. We were both new to the job and both a bit terrified at the prospect of producing issue number 34, but it went reasonably well and by the time of the millennium issue (Winter 1999) we were confident enough to add gold to the original blue of the front cover. After that we started changing the colour with every issue, but retained the original format. After much sterling service, Craigie left for another job after issue 40 (Winter 2000) and, in the spring of 2000, Sheila Greaves took on the role of Magazine Coordinator, a title we later changed to Executive Editor.

At this point those of us on the magazine Editorial Board were wondering about a much more radical makeover of the magazine and Sheila was instrumental in the decisions that resulted in the new format which we introduced in the winter of 2001, with issue 45. We also changed the name to *Physiology News*. Sheila moved on at the end of 2002 and Linda Rimmer, from the Cambridge office, took over from issue 49 in the winter of 2002. Since then Linda has taken the entire magazine layout in house and we have found another printer. The result is that the page charges for *Physiology News* are half of what they were previously. Hopefully, *Physiology News* can eventually pay for itself through advertising, but that is a goal for the incoming Editor, Austin Elliott, to realise if he wishes to!

In concluding, things have got easier as the magazine has evolved over the last 20 issues. We now have lots more articles in the pipeline, thanks to the efforts of the Editorial Board and I hope that Society Members feel that it continues to provide useful information. For all the brickbats, and occasional typos, the last 5 years have been fun and the experience has led me on to pastures new as a medical writer. Good luck, Austin, for the next few years.

Bill Winlow

# A career for the retired physiologist: 'social' scientist

Vivian Abrahams extols the virtues of a part-time retirement career as a 'social' scientist

*Vivian Abrahams (above) retired in 1995 after 32 years in the Physiology Department at Queen's University, Kingston, Ontario, where he had most recently held the position of Director of the MRC Group in sensory-motor physiology. It was then that he commenced his career as a 'social' scientist. Prior to coming to Canada he held academic appointments in the Departments of Physiology at the Universities of Edinburgh and Pennsylvania, and the National Institute for Medical Research at Mill Hill. He has also served many research organisations including the MRC of Canada, and the Human Frontiers Research Programme. As well as being a member of the Physiological Society since 1958, he has been a member and officer of a number of North American physiological and neuroscience scientific societies. He has been known to create scientific societies where he saw a social need.*

Many hard-working physiologists find themselves pensioned off with 15 to 20 years of life ahead of them, and their senile dementia barely noticeable. Some deal with this situation by simply continuing to work at their previous job. As long as these older folks are productive, quiet and cost-free, or at least very cheap, employers with space to fill will be tolerant of their efforts. But even for these physiologists there comes a time when their labs will be closed voluntarily or involuntarily and the white coat finally hung up.

There are some retirees who find new congenial employment, perhaps running a B & B or working behind the counter at McDonalds.

Next there are those, dedicated physiologists to their last working day, who welcome retirement and walk out of their laboratories with a sigh of relief, relishing the new found freedom, peace and idleness. For these folks there is joy in their lives that there are no longer students to disturb the even tenor of the day, that the ever more intrusive demands of the granting agencies are irrelevant, that tedious experiments that go long into the night and still produce inconclusive results are a thing of the past, and that the demands of Department Heads and Deans can be ignored. If by chance the retiree was a Department Head or Dean, then they will be able to relish not having to contend with inadequate budgets and space as well as faculty, staff and students - all with unreasonable expectations and bad attitudes.

Lastly, there are also those individuals who have spent years planning for their retirement. They have attended all the available retirement planning seminars for the past 20 years. Their finances are in order, their wills written and their burial plots ordered and paid for. They have even ordered the seeds and plants for the garden that they will tend in the recently purchased retirement cottage located at the end of a peaceful lane in the countryside. For them, all those plans for their retirement can now be successfully fulfilled, even if it turns out that they hate living in the country.

At some stage most of these retirees will have some reason to visit the old Department. Perhaps to attend the retirement party of a colleague, to hand out a prize or to participate in the annual Xmas party. Now is the time when they come face to face with one of the realities of retirement. In the very institution in which they laboured for many years at an occupation which was the centre of their lives, they have become a non-person. Their laboratories have not vanished, but there are new names on the doors and the space is now occupied by strange equipment that has replaced old and treasured items. The office that for so long served as a private retreat has a new occupant, who is not known to you and who has rearranged the office so that it is no longer recognisable and has lost its former womb-like appeal. Technicians once deferential are no longer willing to give you anything but a friendly smile, and the treasured secretary who once fulfilled every wish (well, almost every wish) can only now manage raised eyebrows and a punctilious 'hello'. Even the diligent computer technician is now too busy to help and, horror of horror, your name has been removed from the departmental directory board! Your public persona as a physiologist has disappeared. As far as the world of physiology is concerned you have entered the world of has-beens (or, worse still, the world of the never-was). As you digest the shock of this new state of affairs you realise that you are not yet ready to relinquish your old persona.

Welcome to your new part-time retirement career as a 'social' scientist! You now need retraining to become a

***Is it time for the Society to consider 'Emeritus' membership - free or at a reduced rate - for retired Members? We would be delighted to hear views from Members - retired or otherwise - about this.***

new kind of physiologist with a new vocation appropriate to yourself as an older person, retraining that builds on those years of work, that takes from the past, benefits from all your accrued wisdom, and which fits someone with time on their hands and a serious history as a physiologist.

***The physiologist as a 'social' scientist may be defined as someone whose role in science is no longer in teaching, research or administration, but consists in attendance at scientific meetings, attendance which is strongly, perhaps entirely, influenced by the social context of the meeting.***

The criteria, in no particular order, may include: the physical location of the meeting; the relationship of that location to the domicile of friends, or to a favourite restaurant, to a museum, historic sites, discount mall, vineyard, art gallery or ski slopes or even a beach. There are other factors that enter into the decision of the 'social' scientist. Locations which enable the cold of winter to be mitigated or avoided can be of importance. Similarly, locations that permit a fuller enjoyment of the summer months are also important - and this might include opportunities for golf or horseback riding.

***Retirement does not remove you from the great adventure of physiology. It merely changes you from being an active participant to an informed spectator.***

Why, it might be argued, would you need to go to a scientific society


The life and times of Vivian Abrahams have been pictorially described by Frank Helyar, whose cartoon appears bottom left. Frank and Vivian enjoyed their frequent get-togethers - as can be seen from the photograph aove. Vivian Abrahams is third from the right and the late Frank Helyar is seated to his right

meeting to enjoy any of these pursuits? If you need to ski, go to a ski resort. Shopping can be done at home, or perhaps even on horseback. This is true, but there is one really important thing that draws the social scientist to meetings, and it is inherent in the nature of a career in science. A career in science means being part of a shared adventure, an adventure shared with many people. Some of these are physically close, perhaps in the same department, but many of those that you have shared your career with will be located many miles away, often in other countries. Retirement does not remove you from the great adventure. Rather, it changes you from being an active participant to a spectator. Not just any spectator, but an informed one who knows many of the players and many of the problems that are being tackled and who is very interested in the new developments and new ways of thinking. A scientific meeting is no longer about you presenting your latest and newest findings. Instead it is a chance to hear about the work of other people and to do so in the company of friends and colleagues of 30 or more years. It is a time to remember with them old battles and turning points, of the times in a career when cruel decisions had to be made, of triumphs, and of disappointments and mistakes. Even perhaps to recall some indiscretions of youth. Equally important, meetings now can offer a special kind of joy, the joy of seeing a student that one has nurtured now recognised as an authority and playing a major role in science. Even more joy when that student recognises the old mentor, and takes a turn at the bar picking up the bill. It is a chance to meet again the old colleagues who did, and continue to do, work that is amazing. And yes, the science might include a stunningly good, easily understood review lecture that revives the excitement that only good science can bring, or a communication might be presented that, at last, sheds light on a problem that has puzzled you for years.

***Practical tips for the newly fledged 'social' scientist ....***

Being a serious 'social' scientist does require the acquisition of a new set of skills for life on the fringe of science. It is essential to be able to relate sensibly to those who are at the meeting for a more serious purpose. Poster displays are easy to handle. For those posters that are too complicated, poorly understood, or totally incomprehensible, a polite nod to the author in passing will suffice. When, as can happen, a poster discussion has been entered into that has gone beyond your zone of knowledge or has entered the zone of your intellectual rust, an exit may be more difficult to engineer. Perhaps honesty is the best policy in this case. Ignorance confessed, and the farewell ladled with suitable praise for the author's remarkable ability (note: terms like genius are best avoided), an exit can be made. Whatever has happened, once eyebrows are raised it is time to move on.

***....a warm lecture room is a particular hazard....***

A word of warning. Attendance at short communications in a warm lecture room is a particular hazard for the 'social' scientist. Unlike some of the more committed attendees, the social scientist is likely to take meals seriously. This then leads the problem of management of the post-prandial nap, a serious problem exacerbated by the commonly encountered dimly lit, overheated lecture theatre. The problem is not so much that one is unique in being asleep, for so are many other attendees, some even sleeping with their eyes open. The worst problem is when the person chairing the session is known to you and, deciding the session needs some light relief, sees you as a target to be embarrassed without fear of repercussions. There are few things worse than to awaken in a crowded lecture theatre just in time to hear your own name as part of the phrase being uttered from the chair, 'perhaps Professor X would care to comment on that most interesting communication?'. Apart from open confession there is no easy way out. Perhaps the only course of action for the 'social' scientist to avoid such situations is to resist the temptation to attend such sessions and take a rest in the hotel room or some other comfortable and appropriate spot.

In determining whether or nor to attend a particular meeting the 'social' scientist will pay careful attention to the opportunities offered by the social agenda of the meeting. The Society for Neuroscience is most attractive in this respect. Its programme for the meeting in New Orleans in 2003 listed 20 pages of events, many of which were solely or mostly social in nature. How could a 'social' scientist not be enamored of an event designed to allow the person to 'relax with a drink and mingle with guests' or resist an invitation 'to drop by for a cocktail and/or a "toast and roast"? Of course the Canadians at the Society for Neuroscience, always needing to live up to their image of dour responsibility, advertise a 'brief business meeting', but fortunately save themselves by pointing out that 'a cash bar will be open all evening'. Despite the problems created by its sheer size, the Society for Neuroscience could be considered a model for the 'social' scientist. Not only does it offer a plethora of social events, but like many North American Scientific Societies including the American Physiological Society, the Canadian Physiological Society and the Canadian Association for Neuroscience, it encourages attendance by its social scientists by offering retired members emeritus membership. For the member so designated there are no longer any annual fees to pay, and the Society for Neuroscience even waives the annual meeting fee and arranges a painless pre-registration. For all these societies the emeritus member also continues to receive pertinent publications.

Which brings me to an important point. It is now high time for the Physiological Society to make itself more appealing to the retired members who have become social scientists. The Society has recently begun to ask for views on its charitable expenditures. Well, as they say, 'charity begins at home'. Perhaps it is now time for the Society to recognise that it can enrich the lives of the older retired physiologists by making it easier for them to enjoy life as a social scientist. To do so would be simple. All that is needed is to create the category of emeritus membership. This status could be offered to retired members with 30 or 40 years of paid up membership behind them. Emeritus members would be excused from paying membership and meeting fees, and they would still receive pertinent publications. After all, this would be in keeping with the Societies' origins around the dining table. And what dining society would not want to encourage its scientific grandparents to be present at the table? Even if the only reason for the grandparents to be there is to eat dinner.

Vivian Abrahams

## Congratulations to ...

### New Year Honours

Robert Boyd, lately pro-vice-chancellor of the University of London and former principal, St George's Hospital Medical School on his Knighthood. Robert has been a Society Member since 1977.

### EGM elections

At the Extraordinary General Meeting held on 18 December, 2003 during the Cambridge Meeting, David Eisner was elected to Council, and is now the International Secretary. The followng Honorary members were also elected: Geoffrey Burnstock, Sydney Brenner, David Brown, John Coote, Robert Horvitz, Julial Jack, Cecil Kidd, Paul Nurse and John Sulston. (Voting on the Governance documents was postponed until the next AGM following advice from our solicitors and the Charity Commission that a major overhaul was needed.)

### Long serving Members

Work on the latest edition of the Society's 'Grey Book' has highlighted a number of long-serving Members of the Society. We would like to recognise, in particular, those listed below who have remained loyal to the Society for at least 50 years. The length of membership for those achieving 60 years or over is indicated in brackets.

J B Bateman (69), W F Floyd (67), G Brownlee (63), Andrew Huxley (62), Marjorie E Knight (62), David M Greenfield (60), I M Young (60), H M Adams, R J Banister, H B Barlow, Keith E Cooper, J E Cotes, Richard Creese, Eric J Denton, D Dewar, P B Dews, M H Draper, Helen Duke, Frederick N Fastier, P Fatt, Marianne Fillenz, R H Goetz, John Gray, R D Harkness, O F Hutter, Sidney M Hilton, D McK Kerslake, R D Keynes, Peter R Lewis, A S Paintal, J E Pascoe, Stanley Peart, Vernon R Pickles, T A Quilliam, J Murdoch Ritchie, Patricia P Scott, H B Stoner, H J C Swan, John Vane, Owen L Wade, J C Waterlow, T C D Whiteside, Wilfred F Widdas and John G Widdicombe.

## ... and finally, on a personal note, to ...

Hugh Matthews, member of the Editorial Board of *The Journal of Physiology* on his marriage to Susanna Sallstrom; Jo Hancock in the Society's London Administration Office on her marriage to Bruce Rattray; Maggie Leggett (the Society's Deputy Executive Secretary) who marries James Relf (former Society facilities, grants and membership officer) on 27 February; and Elfa Gill (the Society's Council and Executive Administrative Assistant) who marries in March.

# The Journal of Physiology

## A new era

Publication of *The Journal of Physiology* passed to Blackwell Publishing on 1 January, after almost 125 years with Cambridge University Press (CUP). Volume I, No. 1 of *The Journal*, published in March 1878, was edited by Michael Foster (Trinity College, Cambridge), with the assistance of six Editors, contained 10 articles and cost 7s 6d. The earliest statistics on record (1929) show that 85 manuscripts were submitted that year. The Editorial Board now numbers 60, 1,780 manuscripts were submitted during 2003, with around 30 published every 2 weeks.

The Publications Office is now well established in its new location, with 11 remaining members of staff (see panel below).

## New Editors

Recent recruits to the Editorial Board are William Armstrong and Caryl Hill.

William Armstrong writes: 'I was born and raised in Cheyenne, Wyoming, USA. I obtained a BSc in Psychology from the University of Wyoming in Laramie, WY in 1974 and an MSc in Psychology at Michigan State University, East Lansing, MI in 1977. At Michigan State I worked with Glenn Hatton and studied diurnal changes in the morphology of hypothalamic neurosecretory (vasopressin and oxytocin) neurons. I continued with Hatton and received my PhD in 1979, a joint degree in neurosciences and psychology. For my thesis, I studied the organization of efferent projections from the hypothalamic paraventricular nucleus. At that time we were also the first lab in the world to record the electrical activity of neurosecretory neurons from hypothalamic slices in vitro. This work, and my continued interest in the anatomy of this system, brought me to the University of Rochester in 1979 upon receiving an NIH postdoctoral fellowship. Celia Sladek had developed an *in vitro* preparation of the entire supraoptico-neurohypophysial system, and together we recorded simultaneously the electrical activity of vasopressin neurons, and vasopressin secretion from the neurohypophysis.

In 1981, I received a Fogarty International Fellowship to study with Jean-Jacques Dreifuss at the University of Geneva, Switzerland, where I studied the central pathways underlying the milk-ejection reflex. I returned to Rochester as a research assistant professor in 1983, after obtaining an NIH Young Investigator Award. In 1984 I moved to the Department of Anatomy and Neurobiology at the University of Tennessee in Memphis. Here I advanced through the ranks to become a full professor with tenure in 1995. During this time I have been continually funded from the National Institutes of Health. The focus of my most recent research is the plasticity of the electrophysiological properties of oxytocin neurons during different reproductive states. In addition to the research, I currently serve as the Director of the Light and Electron Microscopic Imaging Facility at UT, Co-Director of our Neuroscience Institute, and I teach neuroanatomy.'

New Editors William Armstrong (top) and Caryl Hill

Caryl Hill is a Professor in the John Curtin School of Medical Research at the Australian National University. She obtained her BSc(Hons) and PhD degrees from the Department of Zoology at the University of Melbourne under the supervision of Professor Geoffrey Burnstock. Following a postdoctoral position at the Research School of Biological Sciences at the Australian National University, she was awarded an Overseas Research Fellowship from the National Heart Foundation of Australia (NHF) to study at University College London and then in the Department of Pharmacology at

## Staffing at the Publications Office

The Physiological Society, Publications Office, Building 4A, The Michael Young Centre, Purbeck Road, Cambridge CB2 2HP (Fax:: +44 (0)1223 246858)

| | | | |
|---|---|---|---|
| Managing Editor | Jill Berriman | +44 (0)1223 400181 | jberriman@physoc.org |
| Senior Copy Editor | Carol Huxley | +44 (0)1223 400185 | chuxley@physoc.org |
| Copy Editors | Jonathan Goodchild | +44 (0)1223 400184 | jgoodchild@physoc.org |
| | Lynn Jeppesen | +44 (0)1223 400185 | ljeppesen@physoc.org |
| System Administrator | Dave Gunn | +44 (0)1223 400186 | dgunn@physoc.org |
| Editorial Assistants | | | |
| *The Journal of Physiology & Physiology News* | Linda Rimmer | +44 (0)1223 400180 | lrimmer@physoc.org or journals@physoc.org |
| *Experimental Physiology* | Emma Ward | +44 (0)1223 400183 | eward@physoc.org or ephjournal@physoc.org |
| Senior Distribution Assistant | Ann Watson | +44 (0)1223 400187 | awatson@physoc.org |
| Distribution Assistants | Melanie Parkin | +44 (0)1223 400189 | mparkin@physoc.org |
| | Caroline Rae | +44 (0)1223 400182 | crae@physoc.org |
| | Mary Wilson | +44 (0)1223 400188 | mwilson@physoc.org |

the John Curtin School of Medical Research. Through the subsequent award of a Research Fellowship from the NHF and University positions she continued her research career at the John Curtin School of Medical Research, becoming Head of the Division of Neuroscience in 2003. Her career interests have centred on the development and function of autonomic synapses, more recently focussing on the heterogeneity of vascular responses amongst different vascular beds and the role of gap junctions and connexins in vascular function. She has held positions on committees of the National Health and Medical Research Council of Australia (NHMRC) and is currently a member of the Cardiovascular Health Advisory Committee of the NHF. She has also held committee positions and organized symposia for a number of Societies. She obtained her DSc from the University of Melbourne in 2000 and presented the Edith Bulbring Memorial lecture at the University of Oxford in 2002. Professor Hill has received grant support from the NHMRC, NHF and Australian Research Council equipment scheme.

### Chair-Elect

Nominations for the role of Chair-Elect, to take over from Stewart Sage as Chair in July 2005, are invited. Candidates should be current members of the Editorial Board or members of the Editorial Board who have retired in the past 5 years. Candidates should email Linda Rimmer (lrimmer@physoc.org) by 15 March to indicate their willingness to stand and should send a manifesto (of no more than one A4 sheet) and arrange for a proposer and seconder (who should be current Editorial Board members) to also email Linda indicating their support by the 15 March deadline. Voting will be by single transferable vote from 2 - 30 April, through the London office.

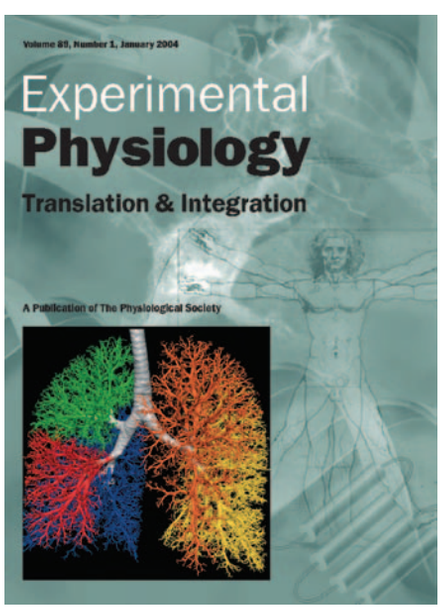
Jill Berriman

*Michael Rennie, Designated Senior Editor on* The Journal of Physiology *until July 2003, with his Head of School as he leaves the Department of Anatomy and Physiology at the University of Dundee after some 20 years. Michael moved on 1 October, 2003 to the Chair of Human Physiology at the University of Nottingham, based at Derby.*

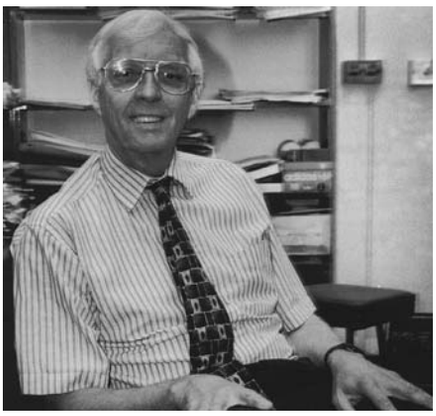
## Experimental Physiology

The most recent meeting of the Editorial Board of *Experimental Physiology* was held on 16 December in Cambridge, immediately before the Meeting of the Society. The Editors, together with representatives of the Society and Blackwell Publishing, came together on a chill evening, a far cry from the last meeting which had been in the middle of a heat wave in Dublin. The meeting was chaired by John Coote who welcomed in particular Torben Clausen and Mike Spyer who had been appointed to the recently created panel of consultant editors, Keith Channon, a new editor, and Liz Marchant and Edward Wate from Blackwells.

With the first copy of the journal from the new publishers about to appear, it was an exciting time to be meeting. We were presented with the final cover design (pictured right) in sage green with a number of muted images reflecting 'translation and integration', the most clearly distinguishable being the Vetruvian man. A figure from the first review article was also inset, which was particularly appropriate as the article on computational physiology and the physiome project encapsulates the new direction of the journal. In order to maintain the quality, authors are being asked to submit potentially suitable cover figures. It was decided to publish manuscripts online at the accepted stage for a trial period of one year as there were still reservations concerning the possible publication of errors. It was also decided that the offer of making the January 2004 issue free online for 2 months should be extended to 12 months.




It was reported that there were also new initiatives being introduced for the provision of journals in the developing world for a nominal sum, or free and this was supported. The Board was delighted to hear from the Treasurer that the archive material (pre 1998) of both the Society journals is to be made available electronically in the future. At present the Society does not hold a full set of E*xperimental Physiology (formerly The Quarterly Journal of Experimental Physiology)*, but Society members are being asked to track down copies of the issues listed on p. 23. The scope of the journal is being revised as, with the online publication ahead of print, there will be no requirement for Rapid Communications. Rod Dimaline had been appointed as the first Hot Topics Editor, a position he will fill from 2003-2007. It was agreed that the aim



EP Chairman, John Coote, was made an Honorary Member of the Society at the EGM in December

should be to publish one hot topic review per issue and that it should be the opening article. Six hot topic reviews had already been published and more had been commissioned. It was felt that Special Interest Group symposia and Focussed Meetings would provide a means of identifying attractive areas and potential authors. Sessions in the Cambridge Meeting had been identified as possible sources.

The Chairman thanked the Executive Committee of the Society for its support of the journal and its aim to define an area for itself. The manuscripts submitted to *Experimental Physiology* in the past year had covered a broad range of topics and were beginning to reflect the focus of the journal on the 'physiome'. The highest number of submissions were in the area of cardiovascular physiology, which must reflect the activity of some of the Editors. Muscle physiology was one area in which there was a potential to increase submissions and the Board would welcome this following the appointment of Mike Hogan and Bente Pedersen to cover developments in this area.

The Board was encouraged by the prospects for the journal to increase its circulation now that it is being produced and marketed by Blackwell Publishing, whose representatives presented a comprehensive and exciting marketing plan. There were not only sales objectives, but readership objectives, including winning new authors for the journal.

Included in the proposed activities will be a re-launch of the journal in the United States at the Experimental Biology meeting from 17–24 May. Blackwell Publishing will host a reception and there will be an informal meeting of American Editors with any other Editors already planning to attend the meeting.

Mary Forsling

### Free online access to Society journals for Members

We are pleased to inform you that all our Members now have electronic access to *The Journal of Physiology* and *Experimental Physiology* through the HighWire Press portal.

This means that you will be able to view, download and print the full text of articles online, no matter where you are. Setting up access is quick and easy. As both journals are now available under an umbrella access control system with HighWire Press activating your subscription on either journal will allow access to both.

To activate your membership subscription go to either journal home page (http://jp.physoc.org or http://ep.physoc.org) and click on Subscriptions. Follow the Physiological Society Members link. Your Subscriber Number is your membership number (prefixed by TPS (the Physiological Society) – no space after TPS). If you have any problems please contact subscriptions@physoc.org

## Council activities

Council meets three or four times a year to discuss strategy and any necessary housekeeping issues. The Magazine Editorial Board recently suggested to me that a regular article in *Physiology News* would be a useful way of keeping Members informed of Council activities. Comments on current activities, or suggestions for topics Council should discuss, are always welcome and can be sent direct to me or to David Sewell at the London Office.

The meeting in November was the first chaired by our new President, Alan North. At his suggestion housekeeping issues were dealt with quickly to allow most of the time for a discussion on long term strategy. The current strategic plan, available on the website, is now 6 years old and should be revised over the next year or so.

To begin this process, break-out groups discussed how changes in the following might affect the future of the Society and how we should respond or plan for them: a) publishing income resulting from the electronic revolution; b) our relationships with kindred societies overseas; and c) our relationship with the Biosciences Federation.

A report from the Members' survey (available in full on the Society's website) fed into these discussions. Useful proposals from the break-out groups included novel sources of income, a desire to raise the profile of the Society in the USA, and a commitment to continued strong support for the Biosciences Federation. Specific strategies will now be devised by the Executive Committee. Members will be consulted again for their views later in the year.

Other items on the agenda included the forthcoming Bristol Meeting and new grant schemes, all of which are described elsewhere in this issue (p. 42) Council will next meet in February, and a report of that meeting will be included in the Summer issue of *Physiology News*.

Dafydd Walters
*Chairman of the Executive Committee*

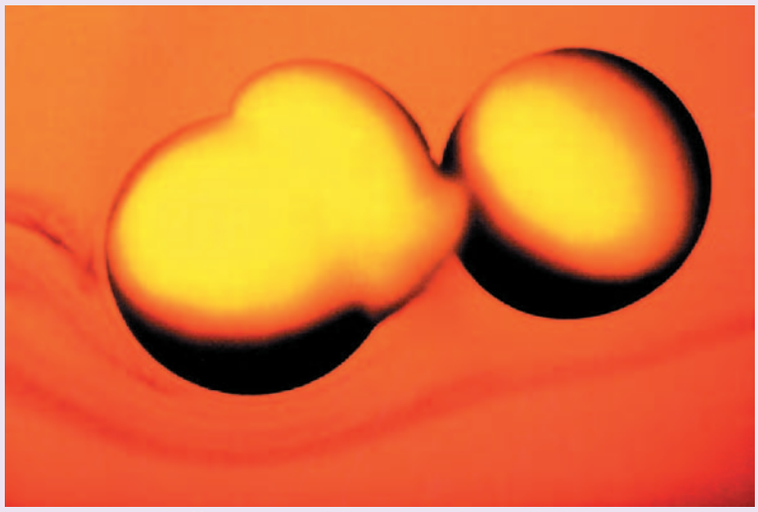
# Nobel Prizes 2003

Ion channel structure, and the way that this confers function, accounted for this year's Chemistry Nobel Prize, which went jointly to Peter Agre (Johns Hopkins) for his work on aquaporin water channels, and Rod MacKinnon (Rockefeller University) for his work elucidating the structure of $K^+$ and Cl- channels. Both Nobelists have been invited speakers at Physiological Society Meetings in the last few years.

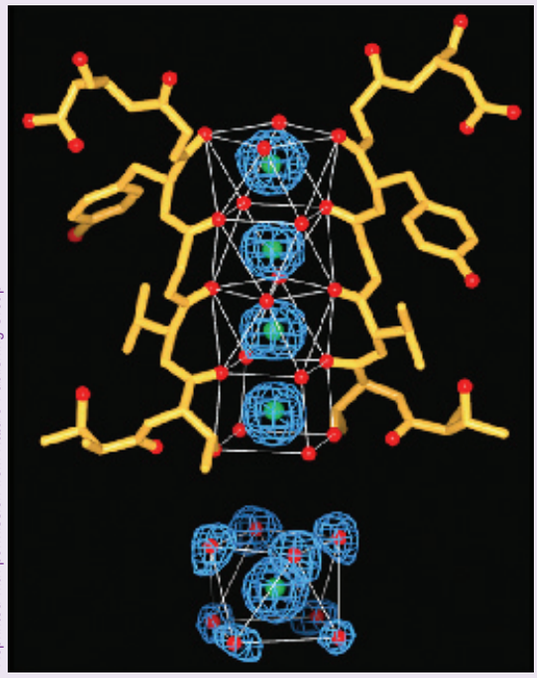
A review by Peter Agre and his colleagues, based on a lecture given at *The Journal of Physiology* Synthesium on Water Transport Controversies at the 2001 Christchurch IUPS meeting (see *Physiology News* **45**, 10), can be found in *The Journal of Physiology* (2002, **542**, 2–16). Rod MacKinnon recently gave a brief summary of some of his $K^+$ channel work in *FEBS Letters* (2003, **555**, 62–65), while recent papers from his lab describing the possible molecular basis of voltage-sensing, can be found in *Nature* (**423).**

This year's Nobel Prize for Physiology or Medicine went to Paul Lauterbur (USA) and Peter Mansfield (University of Nottingham) for their work in developing magnetic resonance imaging (MRI). MRI has been of tremendous impact in medicine, and has also been important in research, especially the functional MRI techniques used to detect regional brain activity non-invasively. Neither of the two MRI winners is a physiologist, though both have at least some physiological connections.

Austin Elliott



An aquaporin-expressing Xenopus oocyte (left) and a control oocyte (right) after placement in water. Image supplied by W Guggino, G Preston and Peter Agre



Reprinted with permission from Nature Publishing Group

Potasium channels allow the selective movement of $K^+$ across cell membranes. Rod MacKinnon's high-resolution structural studies have provided details about the mechanism by which these channels allow the passage of $K^+$ so rapidly and selectively. The image shows four binding sites in the channel's selectivity filter, that two $K^+$ ions can occupy at alternate positions at any one time, and a hydrated $K^+$ in the cavity below

**An interview with Paul Lauterbur, Nobel Prize Laureate 2003 for Physiology or Medicine, will appear in the next issue of *Physiology News*.**

# New Affiliate representative for *Physiology News*

Laura Blackburn (pictured left) has joined the magazine team as the Affiliate representative.

Laura is working on her PhD thesis on the neurobiology of phase change in the desert locust in the Department of Zoology at the University of Cambridge.

She would welcome contributions from Affiliate Members for possible publication in *Physiology News* and can be contacted at lmlb2@cam.ac.uk

# Obituary – Department of Physiology, University of Birmingham

The department has ceased to exist as a unit. Most of the space which it has occupied is being bulldozed to build a new lecture theatre, a cafeteria and rooms for small group teaching

Dear Editor,
Many - or at least some - of you, will remember the 1000th meeting of the Physiological Society in December 1999 in Birmingham. This very important and unique meeting was held in the Department of Physiology as a tribute to the role played by the department in the development of physiology in Britain. I am sorry to report that this was definitely the last meeting to be held in a physiology department in Birmingham, as the department does not exist any more. There has been reorganisation of the basic science departments involved in teaching medical and science students all over the country with various forms of amalgamation. According to the reports in this bulletin, physiology always came out more or less unharmed and preserved as a field, but this is not the case in Birmingham.

Physiology has a relatively long history in Birmingham. The first course started in 1825 and was attended, among others, by William Bowman in 1832-1836. I do not want to bore you with far too distant details, but would just like to mention that the University created a Bowman Chair in Physiology in 1948. The department became a very well known department in the country for its leading role in the integration of neurophysiology and cardiovascular physiology under Professor Sidney Hilton, who was appointed to the Bowman Chair and the Headship of the department in 1965. When he came to Birmingham there were six members of staff to teach 120 medical students, and very little research was going on at that time. By 1966 the number of staff had increased to 13 with graduate students, postdoctoral fellows and visitors from various countries in Europe, Africa, South America, Australia, Asia and, later on, from the USA as well. In 1972 the intake of medical students was increased to 160 a year with about 70 additional students of dentistry and 30 students who studied physiology for their honours degree. Tutorials were held once a week; thus, members of staff had very close contact with the students with five, and later 10, students in a tutorial group.

However, as everywhere else, since 1980 it has been impossible to replace members of staff who left (three members were appointed as heads of departments elsewhere in the country, some died and others retired), while the number of students increased. The size of the tutorial groups increased but it was still possible to maintain practical classes and the standard of teaching in physiology and pathophysiology as a subject, so that the medical and dental students had a good understanding of the body functions when they entered their clinical years. This became more and more difficult as the number of students increased (in 2003 there are about 360 medical students, 70 dental students, 80 BMedSc students and 50 students for a degree course in nursing), while the number of physiology academic staff decreased to 12.

The strength of the department is/was the result of a good collaboration between specialists in different fields (neuro- and renal, neuro- and cardiovascular, etc.). The gradual addition of modern methods in molecular biology and studies on transgenic mice is enabling the new knowledge acquired on isolated cells or systems to be applied to the whole animal, and eventually to be used for clinical purposes. However, this will be very difficult, if not impossible, in the future due to the imposed changes in organisation.

The reorganisation of the Medical School into divisions was the first step in destroying the integrity of the department, with neurophysiology being in the Division of Neuroscience and physiology becoming a part of the Division of Medical Science.

Further, forthcoming physical separation of cardiovascular physiology from other remaining groups contributes to greater disintegration. The final blow came when the Bowman Chair of Physiology was disestablished after the last Head of Department, John Coote, retired at the end of September 2003. Without consultation with the members of staff the department ceased to exist as a unit. This is even more evident now when most of the space which the department occupied is being bulldozed to build a new lecture theatre, a cafeteria and rooms for small group teaching (ignoring the fact that there are already some existing facilities within the Medical School).

Those of you who were here for the meeting in 1999 might remember that there were six lecture theatres, one of which was enlarged at a cost of several hundred thousand pounds to accommodate a greater number of students (albeit not 360). This theatre has been now rebuilt to convert it into laboratories (at a cost of £2 million) to

accommodate groups involved in cardiovascular research, with smaller laboratory space and very little office space. The rest of the physiology staff will be relocated in different parts of the Medical School, which would make contact between workers even more difficult. Nobody seems to know much about the future location of departmental facilities which served everybody (such as histology and image analysis) or the secretaries – if there are any left. There is no provision for a seminar room and the one physiology used to have, where its library and projection facilities still are, is now locked and can only be booked centrally – but no more access to the library or meeting with colleagues.

Thus, not only has the department disappeared as a unit, but the future of integrative physiology in Birmingham, where it was very strong, is threatened. It is very easy to imagine that molecular biology is all we need and to forget that it will ultimately be necessary to apply the knowledge to the whole organism. Let us hope that, by the time this is required more than today, there will still be some people capable of performing experiments on whole animals. However, I doubt that this will be in Birmingham.

It might all appear to be a bad joke, or a deliberate attempt to destroy physiology as a discipline in Birmingham, but for the people who have been associated with the department for decades, it is a very sad state of affairs

So please, remember the department as you saw it in 1999 and wish it REQUIESCAT IN PACE.

Olga Hudlicka
*Professor Emeritus*
*University of Birmingham, Birmingham, UK*

## Getting it wrong

Dear Editor,
While reading the article on 'Receptors and cell signalling on oxidative stress' (Physiology News, 53, p 39), I noticed that one of the pictures is incorrectly labelled 'The Hungarian Academy of Sciences (top)'. The picture was taken from a building which is under reconstruction to become a hotel standing on the Pest end of the Chain Bridge (Lanchid), while the Hungarian Academy of Sciences is situated to the left in an even more impressive building (not shown).

I am delighted to hear that the conference was a great success, just as was the joint meeting two years ago.

Zoltan Molnar
*Department of Human Anatomy and Genetics*
*University of Oxford, Oxford, UK*

## Getting it right?

Dear Editor,
I would just like you to know how well done I think the current issue of *Physiology News* (number 53) is. It definitely fills a void in making us aware of developments in areas of physiology that we haven't kept up with otherwise.

Gerald Westheimer
*(Member since 1964)*
*Department of Molecular & Cell Biology*
*University of California*
*Berkeley, CA, USA*

## ...and again

Dear Editor,
I would like to say what a cracking number of *Physiology News* the Winter issue was (number 53). There were several articles, all informative and easy to read. Some of this material will find its way into my current teaching. I look forward to the next issue. I hope you continue to get further papers of a similar quality.

My one regret is that nobody seems to want the 'big blue tank' that features in the Readers Advertisements in that issue (p. 51). I shall have to investigate its possible uses in microbrewing!

John Mellerio
*School of Biosciences, University of Westminster*
*London, UK*

## Beyond the call of duty

Dear Editor,
Your call to reviewers to sign their referees' reports has reminded me of an incident where a reviewer went beyond the call of duty! After I sent an article (Perumal & Rao 1974) for publication, I received a two line letter from the referee stating that the manuscript had been sent to the press editor. For a long time I did not understand the connection, but the obituary in *Physiology News* gave me a clue. Mary Pickford was born in Jabbalpur!

J Prakasa Rao
*Department of Physiology*
*Christian Medical College, Vellore – 632 002*
*Tamil Nadu, India*

Reference
Perumal TA & Prakasa Rao J (1974). Effect of pharmacological blockade on lithium induced water drinking. *Br J Pharmacol* 51, 107-108.

(Post) Christmas competition
Can you identify this well-known UK physiologist (a former officer of the Society) meeting the challenge of playing Father Christmas?

# Organisation of scientific meetings

## Format of meetings

At the last AGM a motion was carried that the Society should move to hosting one main scientific meeting a year, together with a number of focused or themed meetings. It is envisaged that the first of the new-style main meetings will be held in 2006, with the Bristol meeting in July 2005 being a 'transitional' meeting (see below).

The change in format is an exciting opportunity for the Society to provide a high profile forum for physiology in the UK and to create meetings that are attractive internationally. It is critical therefore that the timing and the format of the new-style meetings meets the needs of the Society. To this end we are keen to solicit the views of all Members and have set up a discussion forum on the Society's web site (*http://www.physoc.org/members/*). At this site you will find the background information that led up to the change, a draft proposal for the format of meetings from 2006 onwards, and an opportunity to express your own views and to comment on those of others.

Remember, these are your meetings and it is important that the form they take is determined by you, the Membership.

## Voting on abstracts and publication of *Proceedings*

At a time when the Society, and its meetings, are undergoing considerable change and modernisation, the Meetings Sub-Committee is keen to hear Members' views about voting on abstracts, with the intention of bringing a motion for discussion to the next AGM. We would also find it useful to get feedback on the publication of the *Proceedings* only in electronic form.

Many Members have strong views on these important issues (see for example the letter from Dave Shirley and Matt Bailey, *Physiology News* **53**, 42). You can add your own opinions to the on-line discussion forum.

## Bristol Meeting of the Physiological Society in 2005

At its last AGM, the Council of the Federation of European Physiological Societies (FEPS) agreed to hold its future scientific meetings as part of the calendar of meetings of any one of its 27 constituent societies. The first of the new-style FEPS meeting is to be held jointly with the Physiological Society in Bristol in July 2005. Details of the International Joint Meeting of the Physiological Society and FEPS will be posted shortly on the Society's web page and, at the same time, there will be a call for symposia. The meeting has been scheduled to take place from 20 July (p.m.) to 23 July. The meeting will be preceded on 19 July by a European Young Physiologists' Symposium (sponsored by Pfizer and the Society) and, on the morning of 20 July, by a Young Physiologists' Careers Fair.

Make this a date for your Meetings Calendar in 2005. We anticipate a high level of participation in this new endeavour, which will encompass all aspects of physiological research from Europe and beyond.

## Associated scientific meetings in July 2005

Two focused international meetings have been scheduled immediately before and after the Bristol Meeting (see box below). This arrangement is to enable international visitors to participate in both of the focused meetings and the general meeting.

**'Mammalian Myocardium 2005'**
**17 – 20 July, University of Leeds**
Organisers: Mark Boyett (Leeds), David Eisner (Manchester), George Hart (Liverpool) & Clive Orchard (Leeds)
Web site:
http://www.leeds.ac.uk/mm2005/

**'The Physiology of Anion Transport'**
**24 – 25 July, University of Bristol**
Organisers: David N. Sheppard (Bristol), Michael A. Gray (Newcastle) & Tzyh-Chang Hwang (Missouri)

Bridget Lumb
*Meetings Secretary*

# New grant schemes

## Special symposia

Funds are available for 'special symposia' to honour Members of the Society who have made exceptional contributions to physiology and/or the Physiological Society. Symposia may coincide with the retirement of the Member or may be held 'In Memoriam'. It is expected that symposia would normally be held in conjunction with scientific meetings of the Society; the registration fee would be waived or reduced for Members. Each symposium can be funded up to a maximum of £5.4K. At least 50% of funds are to be spent on scientific activities (e.g. travel and subsistence for invited speakers) the remainder can be spent on social activities (e.g. a symposium dinner). There will be two submission dates per annum (30 April and 30 September) and funds will be awarded on a competitive basis assessed by (a) the contribution made to Physiology and/or the Physiological Society by the Member to be honoured, (b) the scientific content of the symposium and (c) the benefit of the symposium to Members.

A condition of the award is that organisers are expected to submit a short report of the symposium to the Society's magazine, *Physiology News*. In addition, proceedings of the symposia may be considered for publication in *The Journal of Physiology* or *Experimental Physiology*. Publication would be subject to recommendation by members of the Executive Committee and scrutiny by members of the Editorial Board of the relevant journal.

Details and application forms are available on the website at www.physoc.org/meetings, or from Emma Chaffin (email echaffin@physoc.org).

## Network interaction grants

Funds are available for 'network interaction' grants to facilitate communication between research

groupings in the UK and in the Republic of Ireland. The nature of the interaction is not defined precisely but must demonstrate added scientific value to the individuals concerned and may, for example, centre on the exchange of data and/or technical information or be for the generation of collaborative grants. It is expected that the interaction would normally take place at the host institution of one of the applicants and would last no more than 2 – 3 days.

Each network interaction can be funded up to a maximum of £1.25K to include travel, accommodation, subsistence and room hire charges. There are no upper limits on the number of research groups or individuals per application within the budget constraint. Successful applicants will be required to submit a short report on the outcome of the interaction within 6 months of the meeting taking place.

There will be three submission dates per annum (31 March, 31 July and 31 October). Funds will be assessed on the physiological content of the interaction, the predicted novel outcomes of the interaction and the benefit to Members either in specific or general terms. Awards will be limited to one application per research grouping per annum.

Details are available on the Society's web site (http://www.physoc.org/grants) or from Maggie Leggett (email mleggett@physoc.org).

### Pfizer *In vivo* Physiology Grants

We are grateful to Pfizer for providing grants for Members and Affiliates to carry out activities related to *in vivo* physiology. Activities that might attract grants include presentation at meetings of results from *in vivo* research, attendance at relevant workshops, and visits to other labs to do collaborative work or to learn new techniques. Applications for Pfizer grants will be reviewed in the same way as other Society grants; the same forms and deadlines should be used. Preference will be given to researchers in the early stages of their careers. Please specify in a covering letter or on the form that this is a Pfizer grant application. Further details are available on the Society's web site (http://www.physoc.org/grants) or from Maggie Leggett (mleggett@physoc.org).

Maggie Leggett

## The Biller Award

Kathy Biller (née Sewell) graduated in Physiology from Leeds University and completed her PhD studies with David Shirley in the Department of Physiology at Charing Cross & Westminster Medical School in 1998. Kathy was a regular participant in the Society's meetings, contributing actively to both the scientific and social components of our activities. Kathy died tragically shortly after giving birth to her first child, Lara, in 1999. The Biller award was endowed in 2001 through the generosity of Stephen Biller (Kathy's husband) and is awarded biennially, in years coinciding with the England-Australia Cricket Ashes series. Kathy was fanatical about cricket to the extent that their daughter's name was chosen in honour of Brian Lara, the West Indian batsman. The award goes to a young (under the age of 35) worker in the fields of renal and epithelial physiology.

The recipient for 2002-03 is Donald Ward (above) of the School of Biological Sciences at the University of Manchester. Throughout his post-doctoral career, Donald has worked on the extracellular calcium-sensing receptor (CaR), a G protein-coupled receptor that plays a fundamental role in calcium homeostasis by regulating parathyroid hormone secretion and renal calcium reabsorption. His primary areas of interest include the signalling of the CaR, particularly how it differentially alters hormone secretion in various cell-types, as well as its physiological function in the renal proximal tubule. He is currently a National Kidney Research Fund Career Development Fellow. Donald will receive his award and deliver a review of his research at one of our meetings later this year.

Stan White
*School of Biomedical Sciences*
*Leeds University*

## Pfizer Prize winner

The Pfizer Prize winner at the Dublin Meeting was Mark Dallas (pictured above) with a talk entitled 'Evidence for the existence of GABAergic and glutamatergic neurones within the nucleus intermedius with synaptic connections to the nucleus of the solitary tract in rat' (Mark L Dallas, Susan A Deuchars, Carol J Milligan, Dave I Lewis, Jim Deuchars, School of Biomedical Sciences, University of Leeds). The prize was presented at the Society Dinner on 18 December, 2003 during the Cambridge Meeting.

## New Pfizer prizes

All PhD students, post docs and lecturers using *in vivo* techniques and intending to present an oral communication at a Physiological Society meeting are now eligible to enter for the new Pfizer Prize for *in vivo* physiology. Winners will be awarded £500. The Prize will be held at every Meeting in 2004. A shortlist of winners will be compiled over the year and winners awarded at the end. Up to three prizes will be awarded, the first of these at the Glasgow Meeting in March.

Applications forms and further information are available at:

http://www.physoc.org/meetings
or from Emma Chaffin
(echaffin@physoc.org)

## National biology prize for Emily Ferenczi...

Emily Ferenczi, a medical student at New Hall, University of Cambridge who read Part II Physiology in the Natural Sciences Tripos, was awarded the 2003 UK Science, Engineering and Technology Award for Best Biology Student of the Year [sponsored by Cadbury-Schweppes] by the Institute of Biology, at the London Guildhall on 9 September. This was on the basis of her academic record, extracurricular activities and Honours Degree project entitled 'Membrane potential regulation following osmotic stress in amphibian skeletal muscle'.

Emily writes: 'I'd like to thank the Physiological Society for their support in the form of a Physiological Society Bursary through my 3rd year and for the Long Vacation Studentship that enabled me to develop my Finals research project to its full potential'.

Emily secured First Class Honours in all three of her preclinical years, including Finals in Physiology, for which she was awarded the Fulford and Tyars Scholarships by her Cambridge College, New Hall. In addition to being a keenly physiologically oriented medical student, she holds cross country and athletics sporting Blues for Cambridge, rowed and played tennis for her College, represented her county and the East of England in cross country, and Oxford and Cambridge against the USA in athletics, and had been Ladies cross-country captain. In her spare time (!) she played the clarinet in the Cambridge University Wind Orchestra and was vocalist for the Cambridge University Music Society Chorus.

She is now reading Clinical Medicine in New College, Oxford. Emily is pictured here with Chris Huang, who was her College Director of Studies and her project supervisor.

This is the second year running that a physiology student has been given this national Biology award; the 2002 winner was Claire Martin of Gonville and Caius College, who is now reading Clinical Medicine at Cambridge. Claire also read Part II Physiology at Cambridge and completed a project on skeletal muscle excitation-contraction coupling in the same laboratory, reflecting the increasing interest shown by our brightest medical students in the Physiological Sciences.

## ... and Pfizer Prize for Nancy Rothwell

Physiological Society Member Nancy Rothwell (pictured above) was awarded the prestigious Pfizer prize for Innovative Science at a gala dinner at the Science Museum in November 2003. She was awarded the prize, which will be used for research, both for her contributions to neuroscience and for her contributions to the debate on the use of animals in research.

The £50,000 Pfizer prize for Science Innovation is awarded annually to an academic scientist whose innovative research has made a significant impact on the discovery and development of new medicines.

Maggie Leggett

## HUBS Meeting

Too many scientists and not enough support staff, lack of different career structures and career guidance, and problems attracting the best people into science were the main issues covered at a meeting of the Heads of Biological Sciences (HUBS), at the Royal Institution in November 2003.

Professor John Coggins, HUBS Chairman, suggested that universities, driven by the RAE, had got to a situation where most groups were 'top heavy', with too many academics and too few technicians and other support staff. The EU legislation regarding contracts will make it much more expensive to hire short-term contract staff and, although this was seen as largely a positive move, good employment practise had to be balanced against what was affordable. He suggested that there should be three parallel career pathways, for academic scientists, teachers in universities and more technical staff and that universities had to make these equally attractive. This view was echoed and expanded by others – it was widely agreed that the expectation that all post-doctoral scientists will have an academic career had to be expelled. Dr Mark Walport, the new Director of the Wellcome Trust, felt that careers guidance at this level could be achieved by mentoring, although the Office of Science and Technology (represented by Dr Ann McFarlane) values external input as they are allocating funds for transferable skills training both at PhD and post doc level.

Attracting the best people into science is a perennial problem. Despite the increase in PhD stipends outlined by Drs Walport, McFarlane and Yarrow (BBSRC), there is still no financial competition against jobs in the city. Dr

Walport felt that working with schools was very important so that science was seen as an attractive option from a young age. He encouraged academics to become involved with the new Science Learning Centres, which will provide CPD for teachers. It was also agreed that if a PhD and postdoc could be seen as leading to different careers – not just academia – this would encourage more people to take this path, and to have more varied expectations. Recruitment was seen to be a big enough problem to be the subject of the Spring meeting of HUBS.

The Wellcome Trust will be taking steps to ensure it funds the very best young people. In the past, Dr Walport suggested they have been over worried about process, rather than output, and that as a publicly accountable body they should concentrate on the outcomes of their funding – i.e. the success and careers of the young people they fund. There will be a new committee which will not have a funding remit but rather will concentrate on strategy in the light of this approach. Dr Walport also spoke warmly of 4 year PhD schemes, which although highly competitive allowed academic freedom. Dr McFarlane outlined the 1000 new academic fellowships which will be competitive but will lead to permanent positions.

So – fewer, better-funded positions at all levels, with exit routes from academia clearly marked. The high flyers will still succeed. We can only hope that there will be sufficient help for those not at that level of excellence.

*More details about the meeting are available on the HUBS website: www.biohubs.org.uk.*

Maggie Leggett

### Erratum

*Physiology News*, **53**, 46. The article entitled Pfizer and the Physiological Society was authored by Dr Michael Collis, not Samuel Fountain.

## Research Defence Society AGM

The Annual General Meeting of the Research Defence Society (RDS), held this year on 17 November, always follows a similar format: the business of the meeting is concluded very quickly and then generally excellent speakers talk about subjects related to the use of animals in scientific procedures. This year was little different, except that owing to the sad death of the previous President, Lord Perry of Walton, the business was extended to vote and welcome the incoming President, Lord Taverne. Lord Taverne is well known as a supporter of science, particularly with his recent venture to start up the organisation 'Sense about Science', and is undoubtedly an excellent choice to lead the RDS.

The first presentation was given by the winner of the GlaxoSmithKline Laboratory Animal Welfare Prize. This year the prize was awarded to The Norwegian Reference Centre for Animal Laboratory Science & Alternatives, for work on the development of a database of resources. I was surprised to learn that Norway uses more animals in research per capita than anywhere else. The majority of these are, perhaps less surprisingly, fish. On behalf of the Centre, Adrian Smith spoke of his pleasure at receiving the award, and of the value of sharing this information virtually.

Professor Clive Page from King's College then spoke about his research in lung disease, and of the continuing need for animal research. The Reverend Professor Michael Reiss took a slightly different turn in his talk entitled 'How many animals am I worth?' This was both entertaining and informative, although the concept of doing cost benefit analysis as QALY calculations met with some opposition from the audience.

The second session saw Roger Lyons, General Secretary of Amicus MSF highlight some of the problems felt by research workers and the absolute right of a person to go to work without being subject to violence or threats. The afternoon ended with Lord Sainsbury, Minister of State for Science, outlining Government support for biomedical research. He quoted the recent MORI poll showing that over 90% of the public will accept animal experimentation provided certain conditions are met. The conditions they want are actually the legislation that is already in place. The problem is therefore one of communication – doubts and fears of unnecessary or illegal experiments taking place need to be dissolved, and it is up to the RDS, learned societies and their members to work together to make this happen.

Maggie Leggett

## Benevolent Fund

The Annual General Meeting of the Benevolent Fund will take place at 12 noon on Wednesday 28 April, 2004 at the Society's Administration Office in London. All subscribers to the Fund are welcome to attend. For further details, please contact Jo Rattray on 020 7269 5713 or jrattray@physoc.org

### Fund raffle winners

Congratulations to Neil Spurway, who won *Troublesome Words* in the raffle held by the Benevolent Fund on their stand at the Cambridge meeting, and to David Bates who won the raffle at the Society dinner at King's College. A big thanks to all those who took part! The raffle at the Society dinner raised £130, while the raffle on the Benevolent Fund stand raised £142.55.

For more information on the Benevolent Fund, such as how you can support the Fund, or how the Fund might help someone in need, please contact Jo Rattray.

# What next?

## King's College London hosts the 2003 Life Sciences Careers Conference

If someone tells you that they are a scientist, what picture does that conjure up? A white coat, safety specs and rows of test-tubes in a lab? We are told at university that to stay in science the next step is a PhD and then the natural progression is to do a postdoc. Recently I've been thinking that maybe this is not for me, but what else can I use my science background for?

On 1 November I travelled to King's College, London to the Life Sciences Careers Conference 2003 to investigate what other possibilities were open to me. This event was organised by the Physiological Society, and several other life sciences societies, for undergraduate and postgraduate life science students. The programme for the day consisted of a series of talks, a 'cv clinic' and an exhibition.

When we arrived, we were given our name badges and directed to the lecture theatre where the talks were to be held. Firstly, we heard from Karen Maubach from the pharmaceutical company Merck, Sharp and Dohme who talked about careers in large companies. She described to us the drug discovery process and how different scientists are involved along the way. The second session was a joint presentation by Elisabeth Pain (NextWave) and Tracey Holmes (Science Careers). These are two associated websites: NextWave gives information and advice on different careers and Science Careers is a site to help you actually find a job.

Tim Lang, a clinical biochemist from Nottingham City Hospital, spoke to us, after a tea-break, about careers in hospitals; both in the various laboratories and those involving direct contact with patients. Then followed an enthralling talk on teaching in schools by Alan Knott (St Martin's College). As someone who has always thought of teaching as my worst nightmare, he even had me wondering whether it might actually be fun! The last

Top: The Biochemical Society stand
Above: Students finding out more from the Teacher Training Agency

presentation before lunch was by Tim Powell, a patent law solicitor from Bristows. He showed us how we could use our science training to enter into the legal profession, helping companies through the process of patenting their inventions and with litigation procedures when patents are infringed. This is a fascinating career option which I had never thought of and I think everyone there was attracted by the promise of a six figure salary - something none of us would have thought possible in the world of science!

Over lunch we had a chance to speak to various exhibitors who included AstraZeneca, Huntington Life Sciences and Cranleigh Scientific, along with various scientific societies. Anyone who had sent a cv in advance was then given the opportunity to have a one-on-one session with a reviewer to discuss it. I found this an incredibly useful session giving me an insight into what employers look for in a cv and how to 'sell' yourself.

After lunch, the undergraduates listened to a talk on further degrees by Christine Evans (Welsh School of Pharmacy). Meanwhile, Paul Devlin (King's College) gave us some information on postdoctoral opportunities, sources of funding and how to apply for fellowships. We then came back together to listen to a presentation by Lisa Tang from Voluntary Service Overseas (VSO) and Andrea Paterson who had participated in the scheme. Although at first I wondered about the relevance of this talk, I learnt a lot about the possibility of using your training to make a real difference in developing countries. Andrea talked about what it was like to be the most highly qualified person teaching in a remote Rwandan school.

The penultimate presentation was by Claire Ainsworth (New Scientist) who talked about careers in science communication. Personally, I found this one of the most interesting of the day. She showed us how we could use our love of science to get others interested, via journalism, PR and public education. She also talked about careers in editing, publishing and writing for journals and companies. The last talk, given by Gay Buchanan of Lilley Research, was very useful in showing us how to hunt for jobs and prepare for interviews.

I found the day incredibly helpful as it showed me a wide range of careers in which a scientific background can be put to good use. Congratulations are due to Sai Pathmanathan from the Physiological Society, along with the rest of the organising committee, for an excellent conference. Thanks should also be given to the sponsors of the event: NextWave and Science Careers, AstraZeneca, NewScientist Jobs and Pfizer. I would recommend any young life scientist to attend one of these conferences to find out the vast range of possibilities available to them.

**Alison Overbury**
*School of Biomedical Sciences, University of Nottingham*

**Related links**
http://nextwave.sciencemag.org.uk
http://www.ScienceCareers.org
http://www.newscientistjobs.com

# ‘Sustainable People’

## The BA Festival of Science

Many Affiliate Members thought, based on my advertising e-mails, that I had gone to the University of Salford for an event sponsored by British Airways!

The British Association for the Advancement of Science, i.e. the BA, runs a Festival of Science annually. The Festival is the UK’s leading science communication event attracting over 4,000 adults and students taking part in talks, demonstrations and workshops throughout the week. It enables people from all backgrounds to learn more about the latest advances in science, engineering and technology. The Physiological Society usually runs a half-day session at the Festival each year.

The theme for the Festival in September 2003 was ‘Sustainable Science’, and our session was entitled ‘Sustainable People’. We wanted to include some of the new developments in the field of tissue engineering and transplantation, including building new bladders, making new blood, the problems in cross-species transplants and all the possibilities of stem cell science. As our session was included in the 14 to 19 year old programme, it was important to ensure that topics studied in the curriculum were included. Flyers to advertise the event were sent out to all schools and libraries in the region plus the offer of 10 free tickets to attend the session per school on a first come first served basis. Little did I know that this offer would turn my phone line into a ‘hotline’ in the run up to the event!

PhySoc Member Ian Kay (Manchester Metropolitan University) chaired the session and did a fantastic job of making sure each speaker linked well to the next.

Andrew George (Department of Immunology, Imperial College London) started the session with his talk, ‘Do I want a pig's heart inside me?’ Xenotransplantation is one of the solutions to the shortage of donor organs for transplantation. He used the

Speakers at the Festival of Science 2003. From the top: Andrew George, Kishore Bhakoo, Kenneth Lowe and Ian Kay

sub-title of ‘Can pigs fly?’ throughout his talk to highlight the fact that perhaps what we assume to be impossible, is actually possible. Many schools were particularly attracted to the title of this talk, not only from a scientific point of view, but because of the ethical and safety side as well. A particularly useful topic for Citizenship studies.

PhySoc Member Chris Fry (Institute of Urology, University College London) followed with his talk on the subject of ‘Making new bladders’. He described the use of cell cultures, a technique which students are now very familiar with. Professor Fry explained that as there are many situations when organs in the body have to be replaced or augmented to restore function, it is of great benefit to use cultured cells. These cells can be obtained from the recipient themselves to be grown onto suitable supports to generate replacement grafts. This overcomes the problem of tissue incompatibility and the lack of suitable donor organs.

Following the coffee break, Kishore Bhakoo (MRC Clinical Sciences Centre, Imperial College London) spoke about ‘The pros and cons of stem cells in tissue repair’. The use of stem cells is a very current controversial issue often misrepresented in the media. To be able to give a background view of this topic, and going back to basics of why these cells are so important was of immense interest to the audience. As stem cells can differentiate into specialised cell types, Dr Bhakoo demonstrated how beneficial stem cells could be for generating large quantities of any desired cell for transplantation into patients.

Kenneth Lowe (Life and Environmental Sciences, University of Nottingham) ended the session with his talk entitled ‘Artifical blood: fact or fiction?’ Dr Lowe began his talk by asking the audience if they had ever donated blood. Quite a number of hands were raised. But then when he asked if anyone went back to donate again, only a few hands remained in the air. It would seem that few people were interested in continuing to donate blood. Also those that had a donor card, very rarely carried it with them at all times. This led to Dr Lowe’s description of the search to find effective artificial blood substitutes made from natural and synthetic products.

Teachers and students who spoke to us following the session were pleased to have been informed of the event, and felt the information was extremely useful.

One teacher mentioned that she found it helpful to show her students the types of projects that scientists are working on and why their research is so important.

Another mentioned it was a way of enticing students into the world of

science, as the talks were easy to understand and entertaining.

Soon after the session ended, speakers were grabbed for a press conference and to be interviewed by individual journalists: those from national newspapers, science reporters from *BBC News* and even the *Australian Broadcasting Corporation*! There was also the chance for the speakers to chat informally with students who attended the talks, in a session known as "'**Ba**ckchat'. The students then put together salient points from each talk and presented this to the rest of the group.

The theme at next year's Festival, to be held at the University of Exeter is 'The responsibility of being a scientist'. If anyone is interested in knowing more about the BA Festival of Science, or how to get involved, please contact me on 020 7269 5727 or e-mail spathmanathan@physoc.org.

Sai Pathmanathan

## Biosciences Federation

Members will know that the Society was a founder member of the Biosciences Federation, and continues to support its activities. This column highlights some of the recent events and successes; more information can always be found at http://www.bsf.ac.uk.

### Parliamentary launch

All the feedback that we received shows that the launch was considered to be highly successful. The event drew some useful media coverage, in which the Federation was likened to FASEB in the US.

### Change of President

The Parliamentary launch was somewhat of a swansong for Colin Blakemore, who retired as President to become Chief Executive of the MRC. We wish Colin well in his challenging new post, and warmly welcome his successor Professor Sir Tom Blundell.

### Education colloquium

It was important that the first open event organised by the Federation went well, and the colloquium fitted the bill nicely; an enthusiastic audience of about 200, a highly relevant programme, good speakers and lively debate. The event looked at the communication between school teachers, government and universities in preparing pupils to study biosciences in higher education. The colloquium was largely organised by the Society. A paper on the issues raised will appear in the Spring issue of *Science in Parliament*.

### Letter to the Prime Minister

In December the Federation wrote to the Prime Minister about the Honours list controversy. At time of writing we are still awaiting a response.

### Policy activities

Mike Withnall, Catherine Joynson and Vernon Barber have been busy compiling policy responses all of which can be viewed on the website. Mike also compiles a monthly digest of science policy reported in the newspapers, which is also accessible via the website.

Maggie Leggett

## Handover of the Presidency

In his President's address to the Annual General Meeting in Manchester, Colin Blakemore started by stating it had been an honour and a privilege to be the Society's first President. He stressed that the Members of the Society should be proud of the influence the Society wielded, influence that belied the Society's relatively small membership and went well beyond just UK university science. Colin also noted that the Society was now truly international, as attested by the fact that a third of the current Members were based outside the UK.

Colin went on to pay tribute to the Society's officers, and to the staff members in both London and Cambridge, for all their work during his time in office, during which there had been several major changes to be successfully negotiated.

Colin also commented briefly on the role of the Society's President. It was a good thing, he felt, that the President chaired meetings of the Society's Council, since this gave him a clear hands-on role but did not interfere with the day-to-day running of the Society by the Executive Committee.

Colin finally expressed his regret that he would be leaving before completing his full term, although he felt sure that the Members would understand his reasons. He concluded by welcoming Alan North as his successor.

Alan North then spoke briefly, first reiterating Colin's words about how honoured he too felt to be President of the Society. Alan said that he saw promotion of the discipline of physiology as a key role he hoped to play as President. Working tirelessly to promote physiology as a distinct, though not separate, scientific discipline was absolutely critical for the Society, he said, and ever-more so in an era when departments of physiology on the old model were now scarce. The Society and its President needed to be pro-active in promoting awareness and understanding of physiology, not just within academia but to government, industry, and to society at large, especially young people who would be the physiology students and professional physiologists of tomorrow.

Austin Elliott

## Transfer news

**Alan North** has recently been appointed as Dean, Faculty of Life Sciences at the University of Manchester taking up the position in July 2004. He will join David Gordon, who continues in his current position as Dean in the Faculty of Medical and Human Sciences. Apart from being President of the Physiological Society, Alan is currently Professor of Molecular Physiology at the University of Sheffield and Director of the Institute of Molecular Physiology. A detailed profile of Alan appeared in issue 53 of *Physiology News* (p. 44).

**Clive Orchard**, currently Professor of Physiology at Leeds, is moving to become Professor and Chair of Physiology at Bristol from 1 February, 2005.

*Keep us up to date with your movements - send your transfer news for publication in this column to lrimmer@physoc.org*


## So what makes a good physiologist?

Over the years, I have spent a considerable amount of time on selection committees for academic appointments. The question is always how to decide whom to appoint?

It should be obvious – we want the best person – don't we? Well even that is not always the case. I suspect that sometimes the committee doesn't want someone who is too able and might therefore make his/her colleagues look rather ordinary.

The real reason can be hidden, 'Obviously X is bright but I'm not convinced they have the personality to be part of a team' or 'how would they get on lecturing to our first year hairdressing or physiology with gender studies joint honours students?'

But even when the members of the selection committee are genuinely looking for the best applicant, there is a tendency to behave in perverse ways.

The problem is that it is hard to define what qualities one is looking for. To do the selection properly might require reading the applicants' publications and that would be hard work. One could look at the referees' reports on the candidates. However, these are almost always positive. Well, would you nominate a referee who was likely to be rude about you? So what do we do? The usual approach is to seize on easily quantifiable surrogate markers of quality. These often include the amount of grant income raised or the number and quality of papers.

Grant income is an interesting concept. I remember a time when people applied for grants to get funds to do science. In fact, getting grants wasn't always required and 20 or so years ago people could carry out perfectly respectable research funded entirely by departmental money.

These days you need grant money. But remember the crucial distinction between GOOD and BAD money. GOOD money comes from the MRC or BBSRC, whereas the BAD stuff is from a charity. INDUSTRIAL money oscillates between these categories - I can't remember which one it is in at the moment.

So what if you have an elegant hypothesis which can be tested on equipment borrowed from the classroom (apologies – I am showing my age by thinking that the classroom may have equipment rather than simply purveying computer assisted 'practicals').

What is needed is to get a grant employing staff with lots of money for consumables and, ideally, a flash piece of expensive kit. As an aside, I think that this is probably the worst thing that a young scientist can do. At a time when he or she could be carrying out their own work, the macho culture (sorry, I don't know what the politically correct gender-neutral form of 'macho' is) demands that they build up a GROUP. You know what a GROUP is – it's the left hand column of the acknowledgements slide at the end of the talk. The right hand column is for labs that you collaborate with (usually one in California, one on the East Coast of the USA and, for balance, somewhere in Europe also).

OK, so if grants aren't a good index, what about publications? 'Candidate X has some really good papers' is the sort of statement one often hears. Please don't think this means that the speaker has ever read any of these 'good' papers. What is meant, of course, is that there are several papers published in journals with high impact factors. The arguments against slavish following of impact factors are well known but, for the present, just note that it is a good way to avoid appointing physiologists and, instead, select hot-shot molecular biologists who tend to publish in higher impact factor journals.

But it may be much easier to go with the flow and design an objective means to assess candidates. If nothing else it would avoid the need for tedious and stressful interviews.

The objective quality index could be based on the mean value per year of: grant income in pounds/10000 + (number of papers) x(mean impact factor)x(centrifugal factor). By the way, the centrifugal factor is a term that assesses how near an individual author is to either the front (did the work) or the end (big hitter) of the list of authors. We can argue about the exact value of some of the coefficients but once we have agreed on it then not only will selection committees be a thing of the past but so will the RAE. Talk about 'adding value'.

You may think that this is all too mad to implement. But just remember that 50 years ago, the idea of landing a man on the moon would have been met with incredulity and even 10 years ago nobody would have believed that medical students would be sent away to teach themselves….

I rest my case.

---

*The author is a UK-based Professor of Physiology who prefers to remain anonymous. The author also wishes to stress that s/he is emphatically not related to Mark Cain.*

# Marthe Louise Vogt

1903 – 2003



Marthe Vogt , who died on 9 September, the day after her 100th birthday, was a milestone in my life. Her importance as a 'woman in science' increased greatly along with public awareness of the difficulties facing women in the field of science, as documented in my *SET Fair* Report to the Department of Trade and Industry (Parry, 2003). Marthe Vogt stands as a clear role model, an example of the highest possible achievement.

In 1977 I was told by my then supervisor, A D Smith, that the external examiner for my doctoral thesis was to be 'one of the world's greatest neurochemists'. And so it was that in the less than propitious circumstances of an oral examination, I first met Marthe Vogt. At the time I could not perhaps fully appreciate Smith's epithet. The sharp-eyed woman confronting me unfolded page after page of questions ranging from the deepest conceptual issues in neuropharmacology to the accurate plural form of the Latin names of certain brain regions. Such was Vogt's style: rigorous and precise at all levels of science.

From the start of her life, Marthe Vogt's circumstances were underscored by a strong scientific influence. Her parents, Cecile and Oskar Vogt (French and German, respectively), were distinguished neuro-anatomists living in the exhilarating times of turn-of-the-century Berlin. They would have known all the great neurologists and intellectuals of the day. Their daughter Marthe, born in 1903, would have cut her teeth in an atmosphere of curiosity, discovery and debate. She became trilingual in French, German and English. At that time, few girls could aspire to a medical degree and a PhD in chemistry, but Vogt showed early on the benefits of her upbringing by gaining both qualifications.

In the early 1930s she had already become an established pharmacologist and, by 1935, was head of the Chemical Division of the Kaiser Wilhelm Institut fur Hirnforschung (i.e. 'Brain Science') in Berlin. We can only speculate, as in the case of many great scientists, as to what would have been her fate were it not for Hitler. The increasing menace of the Nazis led to the emigration of a complete generation of now famous names: along with many others, Marthe Vogt decided to settle in England. On the award of a travelling Rockefeller Fellowship in 1935, she went to work with the founding father of Pharmacology, Sir Henry Dale, at the National Institute for Medical Research in London. It was from here that a truly classic paper was published (Dale *et al.* 1936), containing the first description of the release of acetylcholine at the neuromuscular junction following stimulation of motor nerve fibres. The effects of denervation, transmitter depletion and the post-synaptic actions of curarine, are all described so that there could be no alternative interpretation. In simpler terms, the team of which Vogt was part proved conclusively that nerves emanating from the spinal cord released a small molecule into the muscles into which they projected, thus causing these muscles to contract: the study had literally identified the chemical basis of movement!

Cambridge in the 1930s had taken on the mantle of the liberal and intellectual Mecca that had belonged to pre-Hitler Berlin. Marthe Vogt moved here, as a Fellow of Girton. It was at this time that another refugee compatriot, the great neurochemist Hermann Blaschko, first met her. 'She was very dedicated to her work', Blaschko recalls. Nonetheless, such dedication meant not only hard work in the laboratory, but also intense debate. This type of interaction was facilitated by the fact that the Pharmacology and Physiology Departments were housed together. Blaschko partly attributes the enthusiasm and conspicuous commitment shown by Vogt and other young Germans to the oppressive regime in their native country. They had learnt to take nothing for granted and even adversity could be viewed positively, as presenting a challenge to succeed above all odds.

From 1941 to 1946, Marthe Vogt worked alongside J Gaddum on the staff of the Laboratories of the Pharmaceutical Society in London. Perhaps the most seminal paper from this period was that produced with Feldberg (Feldberg & Vogt, 1948). Using 'acetylcholine synthesis' as a marker, Feldberg and Vogt demonstrated the regional distribution of cholinergic systems in the brain. This paper was a classic in that it provided very strong evidence that acetylcholine was a transmitter in the brain: hence, for the first time, we were presented with a chemical basis upon which drugs to combat disorders of the brain could be designed. Not only was this finding a dramatic first, but it was, in a sense, ahead of its time. It is now known that the 'cholinergic' marker, acetylcholinesterase, while technically somewhat easier to handle, is in fact a rather unfaithful indicator of acetylcholine at work, whereas the presence of the synthesizing enzyme for acetylcholine, choline acetyltransferase, is the only real proof of a system being cholinergic. Vogt and Feldberg had used the most accurate marker from the outset.

In 1947, Marthe Vogt moved to Edinburgh where she was a lecturer, and later a reader, in the Pharmacology Department – a post she was to hold for the next 13 years. Five years after her arrival in Scotland, in 1952, she was elected a Fellow of the Royal Society, a distinction up to that time only awarded previously to eight other women.

It is perhaps unfair to cite one paper in an individual's distinguished career as the most 'fundamental' to advancing knowledge. However, a strong candidate for particular mention is

Vogt's paper on the 'Concentration of sympathin in different parts of the central nervous system under normal conditions and after the administration of drugs' (Vogt, 1954).

*'It might be tempting to assign to the cerebral sympathin a transmitter role like that which we assign to the sympathin found in the sympathetic ganglia and their post-ganglionic fibres.'*

This is the conclusion drawn from the observation that sympathin (adrenaline and noradrenaline) is heterogeneously distributed in the brain, and that this distribution cannot be accounted for simply on the basis of the presence of these substances in blood vessels. Not only is the identification of sympathin described meticulously in detailed maps, but regional levels of the transmitters are manipulated physiologically and pharmacologically. Vogt had a further scoop in that she had identified yet another chemical in the brain as a transmitter in the communication between brain cells.

It would be no exaggeration to say that the implications of these findings have provided enormous benefits, not only scientifically, but also therapeutically. For the past 20 years, drug therapies for Parkinson's disease, depression and schizophrenia have been developed from the basic premise that the chemical systems at which the drugs are targeted – catecholamines (including sympathin) – are actually present within the CNS. In addition, this paper has also served as a model to the basic scientist: nowadays we are perhaps too enthusiastic in assigning transmitter status to any substances in the brain, and overinterpret the significance of the mere presence of a neurochemical. Vogt's paper, with its meticulous descriptions, rigorous manipulation of experimental paradigm and cautious yet insightful conclusions, serves as a model almost 40 years on.

In 1960, Marthe Vogt moved back to Cambridge as Head of the Pharmacology Unit, Agricultural Research Council Unit of Animal Physiology. This demanding administrative post did nothing to stem her scientific output. Vogt was among the first to demonstrate the actual release of diverse transmitters from the brain *in vivo*, and their sensitivity to acute events such as electrical stimulation and changes in anaesthesia (Portig & Vogt, 1969). Indeed, Vogt's interests were, if anything, diversified to include a deep familiarity with central serotonergic (5-HT) systems. She also kept abreast of new techniques and concepts and incorporated them into her work (Vogt, 1982).

Marthe Vogt (left) pictured in 1954 with Margarethe (Gretel) Holzbrauer (centre) and Mary Pickford (right)

Even now the brain is still a baffling and elusive system that presents the final challenge to the biologist at the conceptual as well as the practical level. Marthe Vogt had the courage, patience and imagination to work on CNS tissue when the techniques and instrumentation for doing so were in their infancy. When she was once asked why her research had covered areas as diverse as steroids in the adrenal gland and the brain, she replied that, from her youth, she had always been fascinated by stress, what it does to the body and how the body responds to counteract its harmful effects. This question is still, of course, one of the most basic issues in neuroscience, at both the scientific and clinical levels. The fact that Marthe Vogt recognized the problem as seminal demonstrates her acute sensitivity to the central issue and her resistance to the safe but restricting confines of studying one transmitter, brain area or technique.

Since her retirement from administrative work in 1968, Marthe Vogt has been honoured time and again: Honorary Member of the American Academy of Arts and Sciences, British Pharmacological Society, Hungarian Academy of Sciences and the British Association of Psychopharmacology; Honorary Fellow of the Royal Society of Medicine; Honorary DSc and, of course, Honorary Member of the Physiological Society. Her entry in *Who's Who* lists her publications as simply 'papers in neurological, physiological and pharmacological journals'. For many of us, however, these papers have provided not only knowledge, but an inspirational basis for ideas and a working model of the scientific method at its best. Smith's epithet was completely accurate (Greenfield, 1993).

Susan Greenfield
*Director, The Royal Institution*

References

Dale HH, Feldberg W & Vogt M (1936). Release of acetylcholine at voluntary nerve endings. *J Physiol* 86, 353-379.

Feldberg W & Vot M (1948). Acetylcholine synthesis in different regions of the central nervous system. *J Physiol* 107, 372-381.

Greenfield S (1993). Marthe Louise Vogt FRS. In *Women Physiologists*, eds. Bindman L, Brading A & Tansey T, pp 49-51. Portland Press, London & Chapel Hill.

Parry B (2003). On women in science. *Physiology News* 51, 28-29.

Portig PJ & Vogt M (1969). Release into the cerebral ventricles of substances with possible transmitter function in the caudate nucleus. *J Physiol* 204, 687-715.

Vogt M (1954). The concentration of sympathin in different parts of the central nervous system under normal conditions and after the administration of drugs. *J Physiol* 123, 451 -481.

Vogt M (1982). Some functional aspects of central serotonergic neurones. In *Biology of Serotonergic Transmission*, ed. Osborne NN, pp 299-315. John Wiley & Sons Ltd, Chichester.

## Robert Boutilier

Died 20 December, 2003
Elected Member 1995

## A D Dewar

Died 2003
Elected Member 1949

## Plasticity in the human nervous system: investigations with transcranial magnetic stimulation

Edited by S Boniface & U Ziemann. 2003, Cambridge University Press. 316 pp. ISBN 0 521 80727 1

Most mornings I don't feel that there is much plasticity in the human nervous system. But we have come a long way since Kant denied the very possibility of a natural science of the mind. Diverse neuroimaging and neurophysiological techniques have developed dramatically in recent years. Positron emission tomography, functional magnetic resonance imaging, magnetoencephalography and transcranial magnetic stimulation, among others, mean that we do now have real windows on the mind, even if our vision is still through a glass darkly. At the very least, modern studies have demonstrated that the model of a rather static and unchanging brain must be discarded and replaced by the concept of one that is dynamically changing and constantly reorganising, however unlikely this may seem at certain times of day. It just goes to show how misleading our conscious experiences can be.

Anyway, this volume concentrates on the use of transcranial magnetic stimulation to examine human neural plasticity. This non-invasive technique uses focal delivery of current into specific cortical areas to produce two general types of effects. Firstly, the response may reflect the normal function of the area concerned, such as a muscle twitch or a flashing light. Secondly, especially when a train of stimuli is used, the function of the target area can be disrupted, creating a 'virtual lesion'. When such interventions are applied repeatedly, the argument goes, analysis of changes in response latency or task performance can be used to infer cortical reorganisation. Obviously, for the un-indoctrinated, this is something of a causal leap of faith. The nature of the leap is underlined by the detailed chapter on techniques of transcranial magnetic stimulation by John Rothwell, which highlights the importance of differing methodologies and interpretational difficulties. As in all walks of life, there is no such thing as a free lunch. Transcranial magnetic stimulation should evidently not be used without appropriate technical expertise, naïvely or with unreasonably optimistic expectations of its capability. Nevertheless, as is demonstrated in other chapters, thoughtful application of the technique does produce intriguing results. For example, studies of developmental corticospinal plasticity have been performed with a view to improving outcomes for children with cerebral palsy. Changes during skill acquisition have been monitored. Adaptations after peripheral or spinal cord lesions have been followed and attempts have been made to improve rehabilitation protocols after stroke. Since it is known that its effects can outlast the stimulus, another line of enquiry has begun to investigate whether it is possible to harness the method therapeutically. Clearly there are many pitfalls, but much that is interesting. This well-referenced volume, written by experts in the field, is a useful source of information on both, for existing aficionados and for those who may want to join in the precarious, but compulsive ritual of peering inside the dark crystal ball of the human head.

John A Lee

## Ion channels and physiopathologies of nerve conduction and cell proliferation

Edited by B Rouzaire-Dubois, E Benoit & J-M Dubois. 2002, Research Signpost, Trivandrum, India. 202 pp. Hardback, no price available ISBN: 81-7736-135-X

This is a densely packed and interesting book, divided into sections on nerve conduction and cell proliferation.

In chapters 1 and 2 the role of internodal axonal potassium channels and the functions of sodium channels are discussed in relation to how natural toxins modify the probability of channel opening. Chapter 3 considers voltage gated sodium channels and nerve conduction pathology with respect to inflammatory autoimmune diseases and in chapter 4 we discover how potassium channel blockers not only modify central nervous conduction but also inhibit T-lymphocyte proliferation and have beneficial effects on experimental autoimmune encephalomyelitis.

Chapter 5 discusses the role of cell calcium activated cascades in relation to developing anti-cancer therapies to limit proliferation, metastatic activity and cell migration. Chapter 6 outlines the role of potassium channels in the proliferation of neuroimmune cells and the prospects of targeting potassium channels in the control of neuro-inflammation, while in chapter 7 the role of ion channels in prostate cancer is reviewed. Considerations of the control of cell volume are central to many of the chapters, but observations in chapters 8 and 9 suggest that volume regulation may be involved in mitogenesis.

The conclusion provides a good summary of a rapidly evolving area.

Bill Winlow

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

An introduction to cardiovascular physiology. J R Levick. Arnold Publishers. pp. ISBN: 0-340-80921-3

Long term potentiation: enhancing neuroscience for 30 years. Edited by T Bliss, G Collingridge & R Morris. The Royal Society, pp. £85/US$135

The neuropsychology of vision. Edited by Manfred Fahle & Mark Greenlee. Oxford University Press, Oxford, pp 344. £65.00 (hardback). ISBN: 0-19-850582-5

The biology of human survival. By Claude A Piantadosi. Oxford University Press, 263 pp. £24.95 (hardback). ISBN: 0-19-516501-2

The central nervous system. By Per Brodal. Oxford University Press, 515 pp. £49.50 (hardback). ISBN: 0-19-516560-8

# NOTICEBOARD

## FORTHCOMING PHYSIOLOGICAL SOCIETY MEETINGS

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

### 2004

* Glasgow: 29–31 March
Newcastle-upon-Tyne 22–23 July
Cork: 1–3 September
Oxford 1–3 October
King's College London: 18-20 December
(Joint Meeting with the Chilean Physiological Society)

* The designated sessions from the Babraham meeting (originally planned for May, 2004) will now be incorporated into the Glasgow programme. Details will be posted on the Society's web site in due course. Symposia are planned in the following subject areas:

- Calcium imaging in smooth and cardiac muscle
- Cell signalling
- Genetic and molecular approaches to investigate spinal cord circuitry
- TRP channels

### 2005

Seville, Spain 10 - 14 February
Sponsored symposia in association with the Spanish and Dutch Physiological Societies
Bristol 20–23 July

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

San Diego, CA, USA
31 March–5 April
IUPS 2005 is being organised by the six member societies of the US National Committee of the IUPS, the American Physiological Society, the Society for Neuroscience, the Microcirculatory Society, the Society of General Physiologists, the Biomedical Engineering Society and the Society for Integrative and Comparative Biology, under the auspices of the US National Academy of Sciences.
Website: http://www.IUPS2005.org

## YOUNG PHYSIOLOGISTS SYMPOSIA

University of Bristol
16 April, 2004

*In Vivo* Cellular Mechanisms of Cardiovascular Disease. More details will be circulated by email and made available on the Society's website. This event is co-sponsored by Pfizer.

---

## MOLECULAR MECHANISMS IN LYMPHATIC FUNCTION OR DISEASE

Four Points Sheraton, Harbortown, Ventura, CA, USA
7 - 12 March, 2004
Website: http://www.grc.org

## TRANSPORTERS AND DRUG RESISTANCE

Cambridge
18 - 19 March, 2004
British Pharmacological Society 2nd Focused Meeting
Website: http:www.bps.ac.uk

## OBESITY: POTENTIAL PHARMACOLOGICAL TARGETS

University of Buckingham, Buckingham, UK
2 - 3 April, 2004
For further information contact BPS Meetings Office.:
Tel: 020 7417 0111
Email: meetings@bps.ac.uk
Website: http//www.bps.ac.uk

## MICROELECTRODE TECHNIQUES FOR CELL PHYSIOLOGY- A WORKSHOP

Laboratory of Marine Biology, Citadel Hill, Plymouth, UK
8 - 22 September, 2004

Electronics, patch clamp intracellular injection, slice recording, voltage clamp, ion-sensitive electrodes, fluorescent indicators, flash photolysis, bilayer recording, capacitance measurement, microscopy and amperometry.

A variety of marine and other preparations will be used to illustrate the possibilities and limitations of these techniques. The workshop is intended mainly for postgraduate students and postdoctoral workers from any biological discipline who wish to learn these techniques for use in their research.

The course fee of £1200 includes accommodation for 14 nights, full board and tuition. Participants are responsible for their own travel arrangements. Some bursaries may be available for students unable to obtain grant support.

The Workshop has been made possible by support from the Company of Biologists Ltd, MRC, BBSRC, the Physiological Society and the Marine Biological Assocation.

The closing date for applications: 30 April, 2004. A meeting to assess applications will occur during May and all applicants will be notified of the outcome.

Pre-course enquiries to David Ogden, Microelectrode Techniques, The National Institute for Medical Research, The Ridgeway, London NW7 1AA

Email: dogden@nimr.mrc.ac.uk
For further information contact Alexandra Angevi:
Tel: 01752 633207
Email: alexa@mba.ac.uk
Websites: http://www.mba.ac.uk or http://www.nimr.mrc.ac.uk

---

### Noticeboard

Notices for the Summer 2004 issue of *Physiology News* should reach the Publications Office by 12 April, 2004 (lrimmer@physoc.org).

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

## The Physiological Society Meetings 2004

### UNIVERSITY OF GLASGOW 29-31 March (Mon-Wed)

Abstract submission period closed

**Symposia:** Calcium imaging in smooth and cardiac muscle; Cell signalling; Genetic and molecular approaches to investigate spinal cord circuitry; TRP channels; Teaching Workshop

### UNIVERSITY OF NEWCASTLE-UPON-TYNE 22-23 July (Thurs-Fri)

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

### UNIVERSITY COLLEGE CORK AND ANNUAL GENERAL MEETING 1-3 September (Wed-Fri)

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

### UNIVERSITY OF OXFORD 1-3 October (Fri-Sun)

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

### KING'S COLLEGE LONDON 18 - 20 December (Sat-Mon)

(Joint meeting with the Chilean Physiological Society)

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