



PHYSIOLOGYNEWS

winter 2002 | number 49

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UCL meeting

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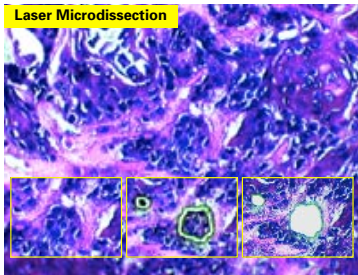
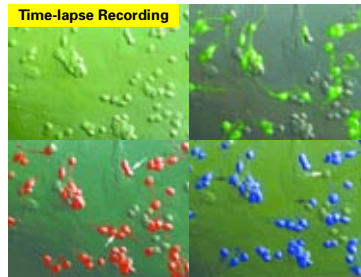
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clinical disease

Labouring to foster Britain's
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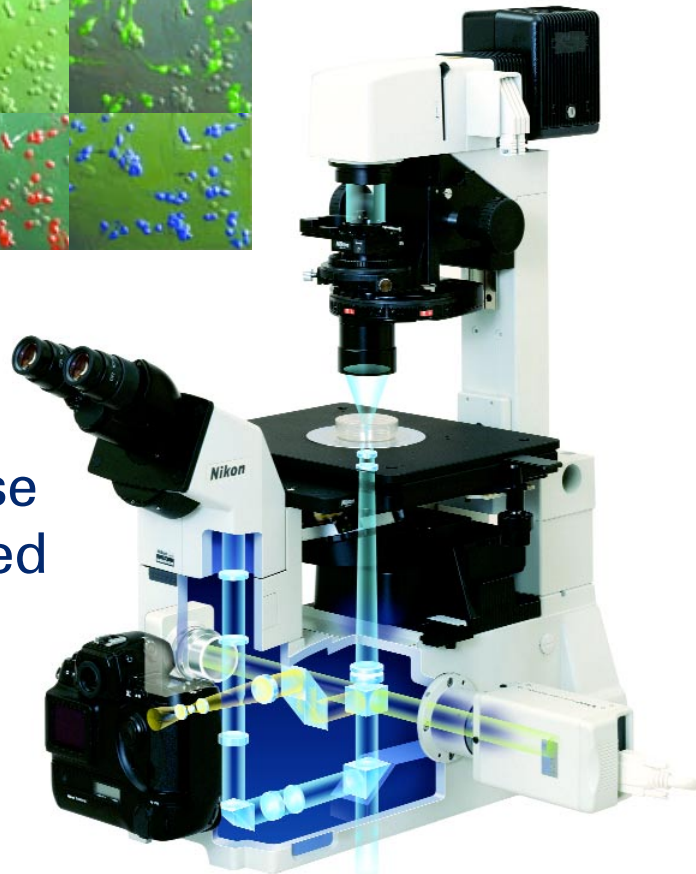
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Cover image



A liberal interpretation of part of Joan Abbott's schematic drawing featured in her article *Whispers in the nervous system* on p8.

PHYSIOLOGY NEWS

Contents

Editorial 3

UCL meeting

Welcome to University College London *Peter Mobbs* 4

Features

Whispers in the nervous system *Joan Abbott* 8

Cellular abnormalities in models of septic shock and in clinical disease *Michael Reade* 12

Labouring to foster Britain's brightest in academia *Bill Parry* 14

Physiological control of behaviour at low temperatures *John Young* 18

MRC and the 3Rs *Vicky Robinson* 21

An update on The Journal of Physiology *Stewart Sage* 22

Society news

Young Physiologists: Current Directions in Exercise Physiology *Ron Maughan* 23

Unbelievable! *Mark Cain* 25

Report of the House of Lords Select Committee on animals in scientific procedures *Maggie Leggett* 26

PostGrad! 26

New grant scheme for affiliate members *Maggie Leggett* 27

Change in policy for *The Journal of Physiology* and *Experimental Physiology* from January 2003 27

Frontiers of Physiological Research:
A Physiological Society Teaching Symposium 27

Application form

Intercalated BSc Bursaries 29

Noticeboard 31

PHYSIOLOGY NEWS

Action Points

Affiliate Travel Grant Scheme:

The next deadlines for receipt of applications are 30 September and 30 November 2002.

BSc Intercalated Bursaries:

The next deadline for receipt of applications is 30 November 2002.

Membership Applications:

The deadline for receipt of applications for full membership is 31 December 2002.

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

Puerto de la Cruz, Tenerife (13-17 February 2003):

Joint Meeting with the Spanish Physiological Society. The closing date for abstract submission is Wednesday 13 November 2002.

University of Newcastle (3-4 April 2003):

The closing date for abstract submission is Wednesday 15 January 2003.

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

Magazine:

Letters and articles and all other contributions for inclusion in the Spring issue should reach the Administration Office by 4 January 2003. Please cite all references in articles in the style of *The Journal of Physiology*.

Magazine Online

The magazine is now available on our website 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 is trying 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 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 2000 words.

Submission of articles

Authors should submit text in the form of a disk accompanied by a printout wherever possible. Use of disks reduces the risk of introduction of errors during re-typing. It is helpful to give brief details of the computer, operating system and software package(s) used.

Deadlines for submission

Contact the Editor's office or the Administration office for submission dates. Late submissions will not be accepted or publication will be deferred to a later issue.

Illustrations

Authors are encouraged to submit diagrams, drawings, photographs or other artwork to illustrate their articles or, if they cannot provide these themselves, to suggest what artwork might be appropriate. Photographs may be colour or black & white, prints or transparencies.

Author photographs

Physiology News normally includes photographs of the authors of articles. These may be colour or black & white; prints are preferable if cropping is required.

Digital photographs and images should be produced at a minimum of 350dpi.

References

Authors are requested to keep the number of references to a minimum (preferably no more than two or three), in the style of *The Journal of Physiology*.

Suggestions for articles

These should be made either to the Executive Editor or to a member of the Magazine Editorial Group (see contents page).

EDITORIAL

PH

Should we press for open peer review?

From time to time all of us submit grants for funding and papers for publication. Sometimes they are accepted, but more often than not they fail. It's very galling for them to be sent back without peer review and often with some anodyne remarks saying "thank you for your grant/paper. We think the work is good quality, but it is inappropriate to this research council/ journal". What really annoys most of us about this approach is that the work appears to have been dismissed out of hand with no apparent reason behind it, because we checked with the research council/journal about acceptability beforehand and closely read all the instructions and obeyed them, didn't we? We then move on to another grant awarding body or journal and this time the area is obviously of interest because it gets sent to referees for anonymous peer review, which is sometimes very constructive indeed. However, now and again potentially excellent pieces of work are blocked by very clever and unnecessarily destructive criticism.

So what's wrong with anonymous peer review?

Many people would say nothing at all is wrong, while others worry, not without foundation, that their very anonymity

allows a small number of referees to make unjustified comments that they would never make if they had to sign their reports or actually say them to the author in person. Occasionally the comments can appear vindictive and some authors complain that their work has been stifled by their competitors, allowing those competitors to gain an advantage in terms of research income or a first publication. It doesn't happen often, but it does happen, even though chairs of grant committees and editors do their best to prevent this state of affairs.

So shouldn't we get rid of the anonymity?

Well yes we probably should, but how do we deal with irate colleagues e-mailing us, phoning us or worse still approaching us at meetings and accusing us of wrongfully dismissing their work. I'm not sure that I have an answer to that, but what I would like is for society members and other readers to e-mail me at wwinlow@aol.com to give me their views on the issue. Please be brief and do not expect a personal reply, but I will publish the results in the next issue, so *Let's hear from you.*

Is refereeing of research papers really necessary?

I have often heard it argued that the cream will float and that good work will always be noticed, so why bother to referee it all, other than to check the

grammar, the suitability of the paper to the journal and that its construction fulfils the guidelines set out. In many respects this is a strong argument, since good work will be recognised by others in the same area. But can you imagine the additional piles of second or third rate papers that we would all have to plough through! Mind you it might wreck the system of impact factors, which might be some improvement!

Many thanks to Sheila Greaves

With this issue we sadly say goodbye to Sheila Greaves, our Executive Editor and a long-standing member of the Physiological Society staff, who has moved on to pastures new in publishing. Sheila has been a tower of strength over her two-and-a-half years as Executive Editor, a critical time of change when we relaunched both the title and the format of the Physiological Society's magazine. Without her efforts I doubt that we would have managed to do it. So to Sheila, good luck in the future and a hearty thanks for all your efforts both for the Physiological Society and for *Physiology News*.

Bill Winlow

Editor

winter 2002 | number 49

Welcome to University College London

Peter Mobbs



The Department of Physiology at UCL is delighted to welcome members of the Physiological Society to the Christmas meeting. The last meeting at UCL, which took place in June 1999, had five symposia and nearly two hundred presentations. It will be a hard act to beat but I have no doubt that the forthcoming meeting organised through the hard work of David Jordan and others will be even busier and more exciting than the last. There will be symposia on the athlete's heart, ion channels, hearing, cell signalling and energy balance, and designated lectures by Erwin Neher, Ian McDonald, Robert Irvine, Gordon Reid, Ingolf Blasig, Roger Adamson and Gordon Smith. These events, and the 9 designated sessions ranging from cardiovascular physiology to cellular signalling, promise an extraordinarily interesting meeting.

Since you can find out all you want about the Department's staff and their research from our website (<http://www.physiol.ucl.ac.uk/>), in this article I have decided not to review all of our activity but rather to concentrate upon what is new.

The changing face of the university

If you came to the meeting in 1999 and come to this Christmas meeting then you will discover just how much the Department and UCL have changed. The rate of change is set to accelerate. In 2000 we opened our new Medical School and Life Sciences Teaching Facility in the Cruciform Building (the former University College London Hospital). These laboratories and lecture theatres are state-of-the-art and have been an enormous success by enabling us to organise our practical teaching more efficiently. Five labs, 4 with a capacity of more than 80, 2 specially designed for 'wet', 2 for 'dry' work and 1 for pharmacology practicals are centrally timetabled and managed by a team of 12 technicians. This organisation means that the real-estate works hard and returns value on the huge initial investment. The technical staff, who used to be employed within the departments of the Life Sciences Faculty, have an environment in which they can share their expertise with others and broaden their skills. The academic staff now have a single point of contact for matters to do with practical classes and the students have a fantastic shiny new set of labs, lecture theatres and computer facilities. Change is never universally welcomed. However, even those who spent longer than most mourning the demise of the Physiology Department's own practical labs have been won over.

Those who have recently spent any time at UCL will know that not all of the buildings are in a wonderful state of repair. Years of under-funding of the UK's universities by government have led to problems with which everyone will be familiar – peeling paint, leaking roofs, rooms that are unbearably hot in summer and equally unbearably cold in winter. I have taken two film crews

The 'Cruciform Building' – home to the Wolfson Institute for Biomedical Research and our new biomedical teaching laboratories



around the Department in the recent past and pointed to loose plaster and the hole in the wall in a lab where 'the snow blows in during the winter'. Fortunately, it hasn't snowed in London in the last few years! However, there is now light at the end of the tunnel and not just that shining in through the chinks in the brickwork, UCL won more than a hundred million pounds in the last JIF round. This money will be of particular benefit to the life sciences; some members of the Physiology and Pharmacology Departments will have new laboratories in a Molecular Neuroscience building currently being erected at the foot of the steps to the 'Institute of Physiology' which was built a hundred years earlier. Physiology's auditory neuroscience group will enjoy new laboratories and increased opportunities for collaboration with colleagues at the Institute of Laryngology and Otology in the new Centre for Auditory Research being built in the Grays Inn Road. Much of the Physiology Department is currently housed in the Medical Sciences Building, the elegant stone edifice that stretches much of the way down Gower Street. The third floor of this will, as part of the Molecular Neurosciences JIF, be remodeled to provide purpose built electrophysiology laboratories.

UCL Physiology has long been at the forefront of developments in cellular imaging. The Physiology Department currently has several confocals and baby confocals, a multi photon machine, and is in the process of purchasing further machines for the JIF developments described above. New JIF funded facilities available in our sister and neighbouring Department of Anatomy and Developmental Biology in the Rockefeller Building include 3 conventional and 2 multi-photon confocal microscopes. Clearly, UCL Life Sciences is set to remain at the forefront in the imaging field. Another JIF development, the Centre for Nanotechnology, will be built near the Bloomsbury Theatre and the Gordon Street

entrance to the central campus. A key element of the science envisaged in the Centre is its connection to the life sciences, especially in the fields of nanodevices for biomedical applications and nanoscale imaging of biological processes.

Earlier this year the Department said a fond farewell to the Physiology Lecture Theatre. The theatre had been in service for most of the period since the Department moved from the building that now houses the Slade School of Art in 1909. Generations of physiology and medical students have listened attentively, and only occasionally slept, thanks perhaps in part to the hard wooden benching, through their lectures in this theatre. Starling, Hill and Huxley all trod its boards. The benches, rickety motorised blinds and squeaky blackboard have now disappeared and been replaced by comfortable seating, computer projection facilities, and improved lighting. Air conditioning, better acoustics and a decent PA system render the need for hard benching as an aid to attention redun-



Top The familiar and tranquil face of UCL

Above Behind the scenes the campus is being turned into a building site. Temporary buildings erected before the last war are demolished to make way for the Centre for Molecular Neuroscience

A computer generated aerial view of the new Centre for Molecular Neuroscience



David Attwell – recently made a fellow of the Royal Society



Michael Hausser – recently promoted to Professor and awarded a Wellcome Senior Research Fellowship has moved to new laboratories in the Wolfson Institute for Biomedical Research



Angus Silver – recently appointed to a Wellcome Senior Research Fellowship



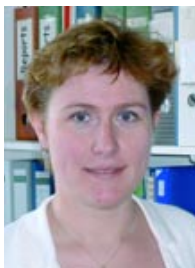
Sandip Patel – a Wellcome Research Career Development Fellow recently appointed as a lecturer in the Department



David McAlpine – a member of the Centre for Auditory Research was recently promoted to a Readership



Paola Pedarzani – recently appointed as a lecturer in the Department



dant. In line with UCL's policy of naming rooms and buildings after famous academics the new lecture theatre has been christened the A V Hill Lecture Theatre. Starling will maintain his presence within it through the recently restored oil painting of him at his bench in the Department in 1927 that will soon hang in the same position it occupied in the old theatre. His former place in the Department, and the continuing presence of Sir Bernard Katz are honoured through the naming of buildings and rooms in the Department and around the campus.

News of new faces and old

The real-estate is not the only feature to have undergone significant change since the last meeting of the Physiological Society at UCL. There have also been major changes in the staff. Mike Spyer, the then Head of Department, has taken over as Dean of the Medical School. Mike, as energetic as ever, continues his work on the autonomic nervous system within his laboratory in the Department on the Royal Free campus. Alex Thompson leaves us at the end of the year to join the School of Pharmacy and replace Trevor Smart as Head of Pharmacology there. Trevor has moved in the opposite direction and is now Head of the Pharmacology Department at UCL. We wish Alex every success in her new job. Sally Page, Barbara Banks, Lynn Bindman, David Allan and Bastien Gomperts have all retired. However, Barbara, Sally and Lynn continue to make significant contributions to teaching in the Department. Though retired, Bastien, together with Peter Tatham, another of the Department's cell physiologists, have written a major new textbook "Signal Transduction".

The Department is delighted to have recently captured David McAlpine from Sheffield, Paola Pedarzani from Göttingen and Sandip Patel from Oxford. All were appointed as lecturers since the last meeting. David McAlpine's research centres on the

binaural processing of sound in the central auditory system and adds significantly to our already considerable strengths in auditory physiology. His presence, the new JIF funded Centre for Auditory Research combined with the already significant strengths of the Institute of Laryngology and Otology, together establish UCL as an international player in all aspects of hearing research. Paola Pedarzani has an outstanding record of contribution to our understanding of the ways in which calcium-activated and other potassium channels contribute to the shaping of action potentials, spike trains and signal processing in the CNS. UCL's traditional strengths in ion channel physiology have also been strengthened by the Pharmacology Department's acquisition of Martin Stocker from Göttingen as a Wellcome Senior Research Fellow – he too is one of the key players in calcium-activated potassium channel physiology. Sandip Patel has a proleptic lectureship in Physiology and currently holds a Wellcome Research Career Development Fellowship. Sandip's research focuses upon signaling by NAADP and adds to an already powerful group of staff interested in the coordination of cellular events by calcium signaling. Steve Harridge, currently a Wellcome Research Career Development Fellow in the Department, has been appointed to a proleptic lectureship. His research on human skeletal muscle function is an important component of the research within our MSc School of Health and Performance.

Other welcome events in the last year included the election of David Attwell to the Fellowship of the Royal Society. David has worked both on the retina and the importance of amino acid transport for the physiology and pathophysiology of the brain. He was pivotal in the generation of the application for the JIF award to fund the Centre for Molecular Neuroscience. Michael Hausser, who holds a proleptic lectureship in the Department, won a

Wellcome Senior Research Fellowship and has recently been made a professor. Angus Silver, another proleptic lecturer, also won a Wellcome Senior Fellowship.

New enterprises in teaching

The teaching front has seen many changes in the past three years. The Medical School launched upon its new 6-year curriculum in September 2000. Students now spend 5 years studying medicine and an additional year pursuing an intercalated BSc. The new medical degree programme is systems-based and integrates basic medical and clinical science with professional skills and competencies throughout the programme. It incorporates all the recommendations of the General Medical Council's report "Tomorrow's Doctors", while conserving the strengths of the pre-existing curricula, many of which were established by members of the Physiology Department including Michael Duchen and Barbara Banks (now retired). Right from the onset, students have clinical contact, with patients, doctors and other health professionals on the three main clinical sites and in community placements. Much of the first 2 years continues to be taught by members of the departments of the Faculty of Life Sciences. For a major new educational initiative the new medical curriculum suffered remarkably few teething troubles and each of the first 2 cohorts of students have commented favourably upon the course.

Last year the Department began a new BSc Programme – Biomedical Sciences. Linda Harrison as Programme Tutor has done an outstanding job in piloting this new degree through its first year. The programme has 50 places and was born out of the recognition that school leavers have increasingly little familiarity with subjects such as Physiology, Pharmacology and Cell Biology. For students unsure of which field they wish to study, the Biomedical Sciences degree programme at UCL provides a solid introduction to a wide

variety of biomedical disciplines and allows students to decide which to specialize in at the end of the first year. The need for such a programme has been highlighted by its success in attracting applicants, in the current year there were 10 applications for every place on offer. Despite increasing student numbers on this new course, the BSc Physiology continues to flourish and it remains a particularly popular choice as an intercalated degree topic.

A further development in teaching has been the establishment of an MSc School of Health and Performance on UCL's Archway Campus. This school, directed by Bruce Lynn, provides advanced teaching in subjects concerned with human health, sport and performance and includes MScs in Physiotherapy, Sports and Exercise Medicine and Sport, Health and Society.

I have used the space available to me here to highlight the many changes the Department has seen over the past three years. However, UCL Physiology remains a hive of research activity and as welcoming and friendly as in the past. I very much look forward to seeing you at the UCL meeting. You will be able to catch up with new research by the old hands as well as that by those new to the crew. We all hope you will enjoy your visit.

Peter Mobbs

Department of Physiology



Top Students at work in the new laboratories

Above A first glimpse of the Centre for Auditory Research

Whispers in the nervous system:

Do glia and brain endothelial cells talk to each other, and if so what do they say?

Recent studies show that astrocytic glia communicate with brain endothelial cells, both to induce properties of the blood-brain barrier, and to regulate barrier physiology. In this article Joan Abbott discusses the mechanisms and implications.



Joan Abbott

Anatomy and physiology of the blood-brain barrier

The blood-brain barrier (BBB) is formed by brain endothelial cells lining the cerebral vasculature. It is crucial in protecting the brain from fluctuations in plasma composition, e.g. during exercise and after meals, and from circulating agents such as neurotransmitters, metabolites and toxins (Abbott & Romero, 1996; Abbott, 2002). The barrier also contributes to the homeostasis of the brain microenvironment necessary for the healthy function of the CNS. Brain capillaries are up to 100 times tighter than peripheral microvessels as a result of tight junctions (*zonulae occludentes*) that severely limit paracellular (tight junctional) diffusion, so that molecular movement is predominantly transcellular. Small lipophilic molecules such as oxygen, CO₂ and ethanol can freely diffuse across the membranes of the endothelium. Small polar solutes needed for brain function are transported by specific carrier proteins (e.g. GLUT-1 for

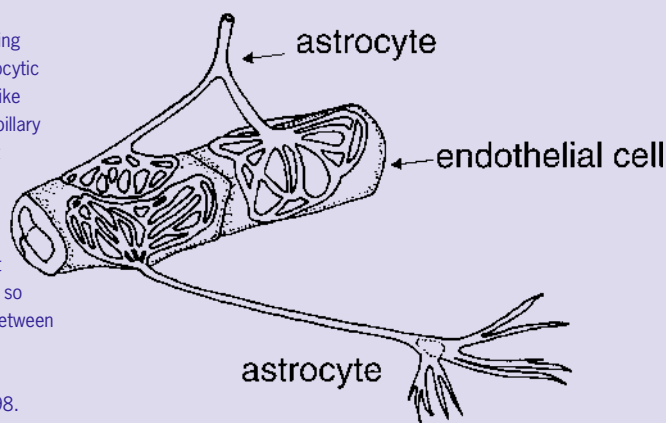
glucose) and specific carriers mediate the efflux of potentially toxic metabolites (e.g. glutamate). P-glycoprotein is a broad-specificity efflux transporter that limits entry of many hydrophobic molecules including toxins. The brain endothelium has lower levels of endocytosis/transcytosis than peripheral capillaries, but has specific systems for transfer of certain peptides and lipoproteins to the brain. The BBB also contains enzymes (e.g. monoamine oxidase) that reduce the central effects of circulating neuroactive agents. Thus the term 'BBB' covers a number of static and dynamic properties that enable the endothelium to protect and regulate the brain microenvironment (Abbott & Romero, 1996).

Induction of the BBB phenotype: role of astrocytes

Certain features of the BBB are also expressed to some degree in peripheral capillary endothelium, but they are upregulated in brain endothelium and hence used as 'markers' of BBB phenotype. There is great interest in the mechanism(s) for this upregulation (Bauer & Bauer, 2000; Abbott, 2002), both for physiological understanding, and to gain insight into pathological conditions, as an important step in designing effective therapies.

The endfeet of astrocytic glia form a lacework of fine lamellae closely apposed to the surface of the endothelium (Kacem *et al* 1998) (figure 1), suggesting that influences from astrocytes could contribute to induction of the specialised BBB phenotype. Early

Figure 1 Schematic drawing showing perivascular astrocytic end feet forming 'rosette'-like structures on the brain capillary surface. This arrangement allows two-way induction and communication between the astrocytes and endothelium, while not forming a physical barrier, so preserving free diffusion between the endothelium and the brain parenchyma. Based on Kacem *et al* 1998.



grafting experiments showed that brain vessels growing into grafts of peripheral tissue became less tight to intravascular tracers, while the relatively leaky vessels of peripheral tissues became tighter on growing into grafts of brain tissue (reviewed in Bauer & Bauer, 2000). Later studies showed that cultured astrocytes could mimic many of the inductive influences of neural tissue. Successful barrier induction and maintenance appear to depend critically on the local conditions and maturational state, with important implications for human therapeutic grafting and for treating brain tumours.

During development the barrier becomes relatively impermeable to large proteins such as albumin and horseradish peroxidase before it can effectively exclude smaller solutes such as mannitol and ions; there is also evidence for gradual maturation of BBB transporters.

In vitro studies have confirmed the key inductive role of astrocytes (Bauer & Bauer, 2000; Abbott, 2002). Freshly-isolated brain endothelial cells and some immortalised brain endothelial cell lines will grow as a monolayer on plastic or on porous filters, and will retain aspects of a BBB phenotype, but generally with some loss of barrier properties (Krämer, Abbott & Begley, 2001). Many barrier features can be upregulated by co-culture with glial cells, including tight junctions, gamma-glutamyl transpeptidase (γ -GTP), GLUT-1, the L- and A-system amino acid carriers, P-glycoprotein, and some endocytotic systems. Interestingly, certain transporters and clotting factors associated with peripheral endothelium are down-regulated in brain endothelium, which could indicate suppression by neighbouring glial cells. Some cultured non-brain endothelial cells also show upregulation of BBB markers under glial influ-

ence, indicating that the underlying processes involve more general cellular mechanisms.

What are the signals from glia to endothelium?

A key question is the nature of the glial influence responsible for induction of BBB features. Some of the inductive effects can be produced by conditioned medium taken from growing glial cells, evidence for action of a soluble factor(s). However, induction is generally more effective where glial cells contact the endothelial basal lamina. Induction appears to depend on the correct apical/basal polarity between endothelium and glia, and may involve the extracellular matrix.

The chemical nature of the glial-produced inductive signal(s) is unclear; it is much harder to detect and identify these signals than for classical neurotransmitters (they 'whisper' rather than 'shout'), since changes are often slow and subtle. Several candidate molecules have been identified (apparently acting on different aspects of the BBB phenotype) including TGF- β , GDNF, β FGF, IL-6 and hydrocortisone. Attempts to isolate the inductive influence(s) from glial conditioned medium have been only partially successful; earlier studies attributed induction to peptides/ proteins, while recent work implicates non-proteinaceous agents of <1kDa molecular weight. Many of the inducing factors have potential as differentiating agents, so the BBB phenotype may represent an enhanced state of differentiation, which can be triggered and maintained by a number of influences, some derived from glia. Indeed, the differentiating effects of intraluminal flow, raised intracellular cAMP or application of retinoic acid are more effective in inducing the BBB phenotype in endothelial cells co-cultured with glia.

In some parts of the nervous system, a blood-tissue barrier is present without astrocytic contact. Thus the microvessels on the pial surface show some BBB features, likely to be due to soluble factors acting via the subarachnoid CSF. Peripheral nerves have effective barriers in the endoneurial capillary endothelium and in the outer perineurium. Since peripheral nerves lack astrocytes, Schwann cells or axons may have equivalent inductive potential (Allt & Lawrenson, 2000). In the CNS, the predominant influence maintaining the mature BBB appears to be astrocytic.

Inductive influence of brain endothelium on astrocytes

Given the complexity of BBB induction by glial cells, it is clear that close communication between endothelium and glial cells must occur. It is therefore not surprising to find that endothelial cells have a reciprocal inductive influence on astrocytes – i.e. endothelium talks to glia. Thus arrays of particles on astrocytic end feet associated with aquaporin-4 are upregulated in co-culture with endothelium. The observed upregulation of γ -GTP in endothelial cells by glia involves a two-way exchange of signals. When endothelial and glial cells are grown together there is a mutual upregulation of antioxidant enzymes so the endothelial-glial partnership copes better with oxidative stress, e.g. in hypoxia/reperfusion injury (Schroeter *et al* 1999). Recently, leukaemia inhibitory factor (LIF) released by endothelial cells of the optic nerve has been shown to induce astrocytic differentiation. Thus maintenance of the adult BBB appears to depend on continuing exchange of inductive signals between glia and endothelium, and disturbance of this induction may be crucial in several neuropathologies involving BBB dysfunction, such as tumours and multiple sclerosis.

Short-term communication between glia and endothelium

In addition to the long-term processes involved in induction via altered gene expression/protein synthesis, glial-endothelial interactions also occur over a shorter time-scale (seconds-minutes). This has been most clearly documented by monitoring intracellular calcium waves, with evidence for ATP acting as a glial-endothelial signalling molecule (Paemeleire & Leybaert, 2000). Such signalling may enable astrocytes to modulate the energy supply to neurons, and to regulate endothelial transport in a way that supports neuronal function.

Humoral modulation of brain endothelial permeability

A number of chemical agents have been shown to modulate the permeability of the blood-brain barrier, including some released by astrocytic glial cells (table 1). The list includes

several inflammatory mediators, consistent with evidence for increased BBB permeability in CNS inflammation (Abbott, 2000). Where the increase in permeability is transient, opening of the paracellular (tight junctional) pathway appears to be responsible. Attention has thus focused on the cellular mechanisms controlling the tight junction and associated cytoskeleton.

Several of the molecules causing barrier opening act via receptor-mediated signal transduction pathways within the endothelium, some involving elevation of intracellular calcium concentration ($[Ca^{2+}]_i$). Although relevant calcium-dependent changes in endothelial proteins have been reported, the details of the molecular cascade are not clear. Examination both *in situ* and *in vitro* is beginning to reveal the details of the signal transduction pathways involving particular receptors and their interactions, for

example for histamine, bradykinin, and nucleotides. In pial microvessels studied *in situ*, B2 bradykinin receptor activation resulted in increased permeability involving free radicals. Activation of cultured brain endothelium by ATP and related nucleotides caused elevation of $[Ca^{2+}]_i$ predominantly via P2U (=P2Y₂) receptors. Interestingly, additional P2Y₁ receptor activation could be detected in cells grown on a biological matrix, mimicking the *in vivo* condition (figure 2), evidence that the endothelial receptor phenotype is influenced by its local environment.

Both *in situ* and *in vitro*, the receptor-mediated barrier opening is generally reversible (Abbott, 2000). This raises the interesting possibility that barrier opening can occur as a well-regulated process under physiological conditions, in response to agents released locally. As the barrier appears designed to protect the brain and maintain CNS homeostasis, would not barrier opening be harmful? There may be physiological advantages in local and reversible barrier opening. Thus the plasma is a rich source of factors required for normal brain repair, including growth factors supporting neurite sprouting and outgrowth in regions of neuronal damage and death. In addition, transient barrier opening could be a good way to maintain immunologic surveillance of the CNS, and for neurons to 'sample' plasma composition as part of the brain's key function in regulatory control of the body.

Quite small stresses to the CNS such as minor injury or surgery cause transient increases in the permeability of the BBB, typically appearing microscopically as focal leaks. We lack non-invasive ways of identifying such BBB leaks, but it is possible that local cyclic opening and closing of the barrier is a normal physiological process. Cyclic barrier activity would have a negligible effect on the general homeostasis of the brain microenvironment, but could satisfy the local requirements that triggered the barrier opening. This idea

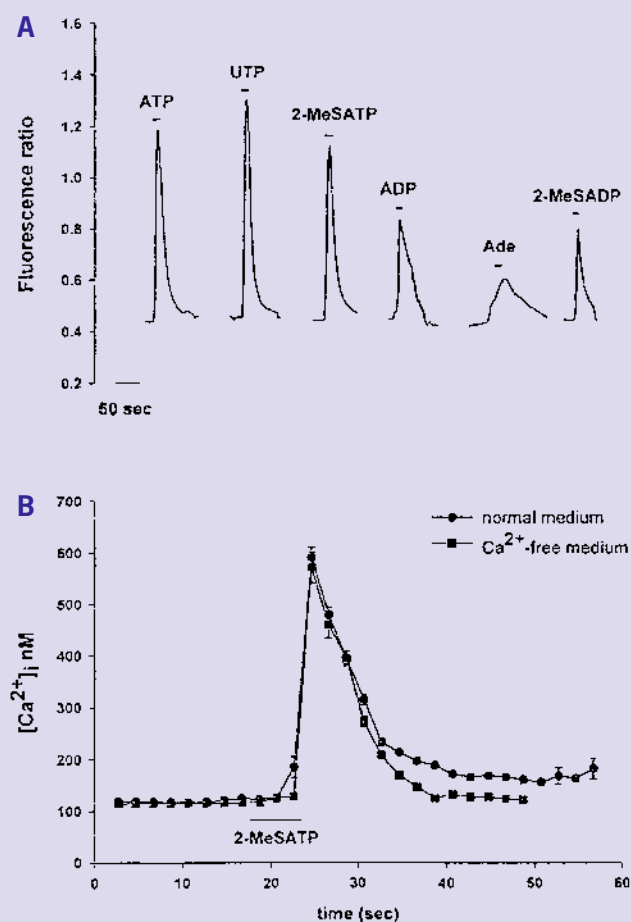


Figure 2 Evidence for nucleotide receptors coupled to elevation of $[Ca^{2+}]_i$ on primary cultured rat brain endothelial cells grown on a biological matrix.

A Calcium responses measured with fura2 (fluorescence ratio) were elicited by 100 μ M ATP and several related agonists; evidence for presence of different receptors includes the observed response to UTP (P2Y₂) and to 2-MeSATP/2-MeSADP/ADP (P2Y₁).

B The response to 2-MeSATP was similar in calcium-free and normal medium, evidence for mediation by a metabotropic rather than ionotropic receptor. From Sipos *et al* (2000) *Br. J. Pharmacol.* 131:1195-1203 with permission.

Table 1 Humoral agents able to increase blood-brain barrier permeability

Bradykinin, serotonin (5HT), histamine, thrombin
Purine and pyrimidine nucleotides: ATP*, UTP, ADP, AMP
Endothelin-1 (ET-1)*
Substance P
Glutamate*, Quinolenic acid
Platelet activating factor (PAF)
Arachidonic acid, prostaglandins, leukotrienes
Cytokines: IL-1 α , IL-1 β *, IL-2, IL-6*, TNF α *
Macrophage inflammatory proteins: MIP-1, MIP-2*
Complement-derived polypeptide C3a-desArg
Nitric oxide*, free radicals

*Asterisked agents have been shown to be released by astrocytic glia.
For references see Abbott (2002).*

prompts a closer examination of the cellular mechanisms that can modulate BBB permeability.

Source of BBB permeability-modulating agents

Since the mechanisms controlling the tight junctions of the brain endothelium are the 'effectors' of BBB permeability modulation, and the chemical agents listed in Table 1 are capable of exerting the modulation, it is useful to identify possible sources of these molecules. In some cases, the endothelium is both able to release and respond to the agent, e.g. endothelin (ET-1), acting on ETA receptors, and ATP acting on nucleotide receptors. Under pathological conditions, mast cells and perivascular microglia (resident macrophages of the CNS) may release inflammatory agents close to the endothelium. Fine nerve terminals of a number of neuronal populations run close to microvessels and release agents such as histamine, 5-HT, substance P and glutamate. Astrocytes are able to release several humoral agents (table 1) although the regulation of this release is not well understood. Furthermore, in response to some of the agents able to open the BBB, astrocytes can upregulate and release modulating factors, e.g. bradykinin causes upregulation of astrocytic expression

and release of interleukin-6 (IL-6), with a potentiating action on bradykinin-mediated BBB opening. Thus in addition to a role in barrier induction and maintenance, astrocytes may play active roles in modulating BBB permeability over shorter time scales. Such potentiating mechanisms also mean that agents present at concentrations too low to open the barrier are able to exert an effect in the presence of low concentrations of potentiating agents.

Conclusions

The development and maintenance of the BBB formed by brain endothelium, and the specialisations of perivascular astrocytes that enable them to act in partnership with the endothelium, involve complex cell:cell exchange of chemical signals, inducing BBB features in the longer term, and modulating cellular physiology in the shorter term. Investigation of this mutual interaction is important for understanding the biological basis of neuropathies in which BBB dysfunction occurs, and in development of effective therapeutic strategies. Physiologists need to listen not only to neuronal 'shouting' but also to non-neuronal 'whispering'.

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Abbreviations

BBB, blood-brain barrier; bFGF, basic fibroblast growth factor; $[Ca^{2+}]_i$, intracellular calcium concentration; CSF, cerebrospinal fluid; ET-1, endothelin-1; γ -GTP, γ -glutamyl transpeptidase; GDNF, glial-derived neurotrophic factor; IL-1 β , IL-6, interleukins; LIF, leukaemia inhibitory factor; MIP2, macrophage inflammatory factor-2; 2-MeSATP, 2-methylthio ATP; NO, nitric oxide; TGF- β , transforming growth factor β ; TNF α , tumour necrosis factor- α .

Cellular abnormalities in models of septic shock and in clinical disease: One example of how rats and humans differ



Michael Reade

Laboratory rats are wonderful animals, with a reputation unfairly tarnished by their ancestors' carriage of the black death. Nonetheless, rodents are the subjects of most studies investigating the pathogenesis of septic shock, presumably because rats and mice are more easily studied than critically ill patients. Therapeutic advances based on this research may well promise new hope for critically ill rats. However there is increasing evidence that human sepsis may be a fundamentally different disease, suggesting conclusions based on animal models may not be applicable to humans.

Shock due to overwhelming infection – septic shock – should be relatively simple to treat. Most micro-organisms that cause septic shock are initially sensitive to a large number of antibiotics, and vascular tone and cardiac output are usually easily manipulated with vasopressors and inotropes. Unfortunately, things aren't that simple, which is why septic shock remains the leading cause of death in non-coronary intensive care with a mortality of around 50%, responsible for the deaths of around 250 000 people every year in the United States.

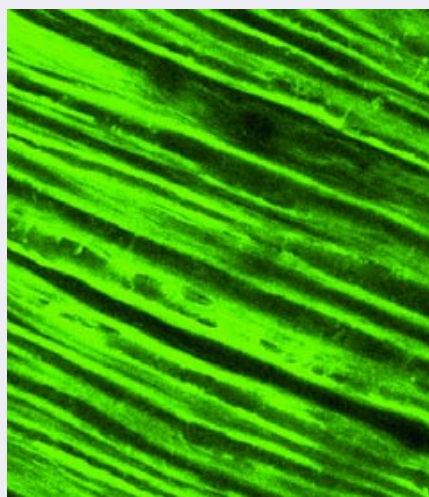
The fundamental problem in septic shock is not the direct effect of the micro-organism, but the generalised inflammation induced in response. Multiple positive feedback loops stimulate the ever-increasing production of pro-inflammatory cytokines and effector molecules. The very large number of parallel pathways involved probably explains the disappointing results of clinical trials that block the actions of individual mediators. A better strategy might be to target the molecule hypothesised to form a common effector pathway for many of these cytokines: nitric oxide (NO).

Nitrate in the urine of febrile patients

was first found to be elevated in 1818 (MacMicking *et al* 1997). However, it was only in 1987 that Ignarro and Palmer, Ferridge and Moncada demonstrated NO was the endothelial derived relaxing factor identified by Furchgott in 1980. Soon after, overproduction of NO was hypothesised to contribute to the hypotension of clinical sepsis. In addition to acting as a vasodilator, we now know NO can further stimulate inflammation, interfere with cellular oxygen utilisation, form cytotoxic free radicals, and act as a negative inotrope. The metabolites of NO are increased in the plasma of patients with sepsis, even when the confounding effect of renal failure is removed. However, the elevation of NO metabolites in human sepsis is nowhere near as marked as in rodents (Pastor & Suter 1998). Rodents have perhaps become more resistant to the effects of NO (as one might if one lived in a sewer), and humans have perhaps evolved mechanisms to limit NO production.

Different whole-body NO production in sepsis is the first warning that animals (or at least rodents) might not be the best models for human disease. A number of other differences are now described. Rat and mouse macrophages reliably produce large quantities of NO in response to a variety of stimuli, making them an easy (and popular) model in which to study the mechanisms of NO upregulation and its effects. That it is extremely difficult to make human macrophages behave in the same way (Schneemann *et al* 1993) is often conveniently ignored. Whilst it is known that circulating peripheral blood mononuclear cells from patients with septic shock do produce a small, but significantly increased amount of NO (Reade *et al* 2002b), it does not compare to the response of rodent cells under similar conditions.

Figure 1 Arterial smooth muscle cells from a control patient, loaded with the NO sensitive dye DAF, which is glowing green in the presence of NO.



Inflammatory cells are a convenient cell type to study, but NO produced in the vessel wall is much more likely to contribute to the shock which characterises sepsis. Endothelium seems to produce less NO in sepsis than in health, even in animal models (Zhou *et al* 1997). Animal vascular smooth muscle cells in culture or studied *ex vivo* can be stimulated to make NO, and increase their expression with inducible NO synthase mRNA. Human arterial smooth muscle cells in culture, stimulated with a very unphysiological cocktail of lipopolysaccharide and cytokines, can be made to behave in a similar manner (MacNaul & Hutchinson 1993). However there are very few studies of vascular smooth muscle from patients with clinical disease – and none that demonstrate with any statistical certainty any abnormality of the NO synthetic mechanism in this tissue.

Obtaining tissue from patients with septic shock is difficult. These patients are very ill, often requiring mechanical ventilation and sedation. Even those able to breathe spontaneously almost invariably have such disordered cognition that they are unable to give true informed consent, either for therapeutic procedures or for participation in research. Where possible in the UK, the assent of a close relative or guardian is sought, but this does not have the same legal status as the informed consent of the patient themselves. The conduct of research on such incompetent patients is very tightly regulated by institutional ethics committees, and what is allowed varies from place to place. For example, whilst in the United States even the collection of data on such patients (such as a review of the medical record) is the subject of some controversy (McRae & Weijer 2002), the European Society of Intensive Care Medicine recommends that the requirement to obtain consent or assent for research may be waived if a number of criteria (such as minimal risk involved for the

patient, the subsequent provision of information about the study when this becomes possible, and prior approval of the protocol by the institutional review board) are met (Lemaire *et al* 1997).

Even leaving aside issues of consent, obtaining vascular tissue from septic patients is especially difficult. The need for 'minimal risk' to the patient essentially means studying tissue removed in the course of a therapeutic procedure. The mesenteric artery is a particularly good candidate, as many patients with a large bowel perforation (and consequent systemic sepsis) require bowel resection, and a piece of the artery can be taken from the pathological specimen. Unfortunately, most molecular and functional studies require at least initial processing of the tissue while it is still fresh. As evidenced by the time stamp on the messages on my pager, most of these operations seem to occur in the middle of the night! And, as every anaesthetist knows, the promise that 'the specimen will be out in about 20 minutes' from the other side of the blood brain barrier (ie. the sterile screen between surgeon and anaesthetist) usually means anything from a 10 minute to 2 hour wait for the hapless research fellow standing by. Not surprisingly, most sensible researchers have stuck to animal and *in vitro* models!

So what has come of these late-night excursions to the operating theatre and pathology dissection room? As reported at the recent meeting of the Physiological Society in Liverpool (Reade *et al* 2002a), in contrast to what is expected from animal models, the expression of iNOS mRNA and protein is decreased in arterial smooth muscle from patients with septic shock, as is its NO production. In the same tissues, inducible

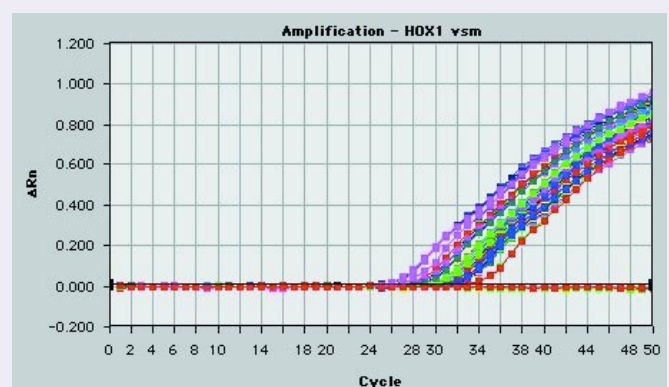


Figure 2 Amplification of heme oxygenase mRNA by real time RT-PCR: fluorescence intensity (and hence product) increase with cycle number.

heme oxygenase (HO-1) expression is increased. Heme oxygenase catabolises the breakdown of heme to biliverdin, which is metabolised to the antioxidant biliverdin. As such, this pathway is becoming increasingly considered a helpful response in cells subjected to oxidative stress.

However, a byproduct of the reaction is carbon monoxide, a molecule with many possible deleterious effects in sepsis. Carbon monoxide vasodilates by activating guanylyl cyclase in a manner similar to NO (albeit with 100 times less potency), and opens potassium channels and decreases synthesis of vasoconstrictors such as endothelin and 20-HETE. Moreover, CO inhibits rat macrophage NOS activity, and inducers of HO-1 suppress the induction of iNOS mRNA by cytokines. If the activity of heme oxygenase is relatively greater in humans than in animals, this may explain the surprising down-regulation of iNOS in arterial smooth muscle, and also the more modest rises in serum NO metabolites seen in humans compared to rodents. If CO is indeed functionally vasoactive in human vessels, blocking the activity of HO-1 may be more effective than the current attempts to selectively block iNOS.

Our study has highlighted a potentially highly significant difference between clinical disease, the animal and *in vitro* human model studies to date. This is not to suggest that animal experiments have no role to play. Indeed, quite the opposite; the next step in our research will most likely involve developing an *in vitro* or animal model which more closely resembles the human *in vivo* condition, to allow further exploration of the regulation and function of these pathways. What it does suggest is that animal or *in vitro* models must be validated as much as possible using tissue from patients with the disease which is ultimately of interest. Failure to do this might well lead to many

novel therapies for septic rats, but no benefit to humans. There is, unfortunately, an ongoing need for researchers gullible enough to carry a pager 24 hours a day, seven days a week ... applicants may apply to the address below!

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Labouring to foster Britain's brightest in academia

The British Government's third Comprehensive Spending Review (CSR) was revealed in July. It was preceded and followed by much excitement, much of it warranted, about this Government's commitment to reversing the decades of under-investment in the nation's science base. In May Tony Blair gave "the first speech by a British Prime Minister dedicated to science



Bill Parry

for more than a generation". He then expressed his surprise of this fact in an article published in the *New Scientist* (27 July). He used the same article to list his Government's tangible commitment to British science by indicating past, and more specifically, present and future monetary allocations and policies designed to augment the current boost to British science.

Beyond the Labour party, the CSR was met by a gush of measured delight from many in academia and a number of science-related organisations. Jonathan Cowie, Head of Science Policy at the Institute of Biology (IoB), announced in a letter to the *New Scientist* (10 August) that the "latest increase in government investment in the British science base is most welcome". Dr Peter Cotgreave, Director of Save British Science, "warmly welcomed the settlement for scientific and engineering research". Dr Rodney Eastwood, Director of Planning and Information at Imperial College, concluded

that this CSR “probably represents the best settlement for science and scientists for some considerable time”.

Professor Nancy Rothwell, Chair of UK Life Sciences Committee (UKLSC), also “warmly welcomed overall the Government’s continued financial commitment to scientific R&D”.

However, their sanguine welcomes came with a number of caveats.

Brain drain or brain gain?

In the Autumn issue of *Physiology News*, three young academic contract researchers from University College London, each at different stages of their careers, expressed their main concerns about their futures in academia. While each enjoyed many aspects and challenges of academia, several issues concerning income and job security (i.e. short-term contracts, short-term funding, low PhD stipends, uncompetitive post-doc salaries, and a poor career structure) meant that they were always open to offers outside of academia.

Did the CSR do much in these areas to stem the threat of brain drain by encouraging Britain’s brightest prospects to embark upon, or stay ensconced within, a career in academia?

I found a mixed consensus: one source was primarily upbeat about the CSR and the Government’s commitments; others readily welcomed the CSR, but added that there was still much more needed ‘to stop the rot’; another influential source – Professor Sir Gareth Roberts – strongly supports the Government’s commitment to the science base, but believes that several initiatives and measures outside the CSR have also been instrumental in bringing about urgent, positive changes.

The details

There have been a number of documents published recently that have alerted the Government to the raft of serious problems that increasingly threaten the UK science base. The most influential, far-reaching and comprehensive of all was Sir Gareth Roberts’ Review, *SET for success*, published in April.

The Chancellor’s CSR was accompanied by a document entitled *Investing in Innovation: A strategy for science, engineering and technology*. Produced in conjunction by the Department for Trade and Industry, HM Treasury and the Department for Education and Skills, the document outlines in Annex A specific recommendations from the Roberts’ Report and measures that this CSR will take to fulfil them.

A number go some way in redressing the concerns the three UCL research fellows made in the last issue, and should make a positive contribution to recruiting and retaining the best in academia:

PhD Stipends

The Roberts’ Report noted and recommended that “the Government and Research Councils raise the average stipend ... to the tax-free equivalent of the average graduate starting salary”.

The Government accepted Sir Gareth’s comments that “it is vital that PhD stipends keep pace with graduates’ salary expectations” and followed its recommendation, saying that it “expects the average

PhD stipend for Research Council students to exceed £13,000 by 2005/06”.

What those interviewed said:

Rodney Eastwood: “The increase in the PhD stipends to an average of £13k is welcomed, as is the flexibility to award higher stipends for those researching in difficult to recruit subjects.”

Nancy Rothwell: “Certainly the increase in PhD stipends is welcome. The demand for PhD places has been declining. This will make Research Council stipends similar to those that have been offered by the Wellcome Trust for several years.”

Peter Cotgreave: “There is a real recognition that, for example, PhD stipends are too low, and they are going to go up to something like the Wellcome Trust’s level, which seems to be enough at present to attract consistently high-quality candidates across the board.”

PhD training elements

Following the Sir Gareth’s recommendation, the Government report stated



that it “expects all universities to meet high quality minimum training standards on their PhD programmes, and agrees that all funding from HEFCE and the Research Councils in respect of PhD students should be made conditional on meeting these standards”. It also announced additional funding to the Research Councils to enable enhanced training for their students.

Academic fellowships

Likewise, the Government accepted the Report’s comments that “there should be a clearer path for those who have completed PhDs into academic lectureships”. The Government will also implement the Report’s recommendations and “provide funds to create 1,000 new academic fellowships (200 a year, each lasting five years) to provide more stable and attractive routes into academia”. It endorsed the idea that those who receive these fellowships should take on an ambassadorial role by actively reaching out to schools, “thereby helping to widen and enthuse the next generation of pupils about science and engineering”.

What those interviewed said:

Sir Gareth Roberts: “Some items in the Recommendations, like these fellowships, we considered more urgent because they would have an immediate short-term impact. This is definitely something that has come out of the CSR that is really important.”

Nancy Rothwell: “The new 5-year fellowships for post-docs on the academic pathway look to be a good idea, but could cause problems for universities in that they will be expected to underwrite lectureships for the fellows very early in their careers.”

Postdoctoral researchers’ salaries

The Government document supports the findings of the Roberts’ Report and its recommendations to make post-doc salaries somewhat more competitive than they have been. It stated that “the Government will fund the Research Councils in the Spending Review to increase their average postdoctoral salary by £4,000 by 2005-06.”

What those interviewed said:

Peter Cotgreave: “The rise in post-doc salaries, and the new money for the HEFCE to ‘implement’ Gareth Roberts’ report, form an explicit recognition that salaries for young scientists have been far too low. Of course, that comes with the caveat that the goal posts are constantly moving, in terms of what non-scientists are earning, so that almost inevitably means that, by the end of the three or four year period that the CSR covers, salaries and stipends will need another boost to catch up, although hopefully nothing like as badly as they do now.”

Nancy Rothwell: “The improved starting salary for early post-docs may encourage more to continue in academic science, although the more astute will look to the future and still see career uncertainty and relatively low salaries at the professorial level. This needs to be considered as part of a package, which also includes improved career management.

“Connected to the issue of recruiting contract researcher staff is the question of lecturers’ salaries, which has been left to the Higher Education White Paper [due for the autumn 2002]. It is therefore difficult to know what influence the Review will have for salaries of

existing academic staff until the White Paper has been published.”

Rodney Eastwood: “We feel that these improvements to pay, training and career support for PhD students and post-docs should help those wishing to pursue a research career. It is unlikely that pay will ever be comparable to what can be earned in the private sector, but at least the government has acknowledged that the need to ensure the supply of highly skilled scientists requires additional resources.”

Short-term contracts and career development

Changes to deal with short-term contracts were well underway before the CSR, says Sir Gareth. The impetus is coming from a number of initiatives in the UK and EU legislation. The Research Careers Initiative (RCI) Strategy Group, which was expanded to include short-term contract researchers, would issue a report in the autumn, Sir Gareth indicated. This will mention a number of initiatives that they have prompted, particularly a Code of Practice for how to better manage contract researchers in terms of career development.

There’s a separate group called HEFCE’s People’s Group, which is working on issues such as gender, research students and the supervision they get or don’t get. It too is issuing a Code of Practice.

Sir Gareth said: “Effectively we have the RCI group, which has focused on short-term researchers; we have HEFCE’s People’s Group, which has been focusing on post-grad students and their supervision. What this will have produced by the end of the

calendar year is some very clear guidance to all university departments on all this. The really important thing is that the HEFCE has actually said that it is unlikely to distribute the people dimension of the Research Assessment Exercise money – the so-called QR money – unless a university has taken this advice fully on board. This is a huge driving force, one of the sticks we've been wanting to put in place to ensure that universities do respond and do manage their research staff in a sensible way."

Another critical driving force is an EU directive, which states that nobody can be recruited on more than two short-term contracts unless there is "objective justification" for doing so.

Sir Gareth is convinced that this will be a major change that will be embraced by British universities: "This is going to make a massive difference. It means that at the end of a four-year period, when a person has had two limited-term contracts, the university is going to have to decide whether to re-engage that person on an open-ended contract or reposition them. So that again is a huge change that has already hit the system."

In its final report, Sir Gareth's RCI group is likely to recommend a new Concordat, asking all universities to abide by the EU directive and the new Codes of Practice generated by the Funding Councils.

"It's going to take a bit of time, obviously, for the culture to change," he comments, adding that it would have eventually changed anyway. "I think these steps will accelerate the whole thing. I'd like to think that in two to three years' time we'll have very few examples of bad practice."

Not all are so confident that the system will be transformed smoothly, however. Peter Cotgreave expresses some optimism, but much less than Sir Gareth: "I doubt whether we will see a huge improvement there [i.e. short-term contracts], but I do believe that the slight swing in the funding balance back towards the HEFCE from the Research Councils means that the situation will at least not get any worse."

UKLSC, while acknowledging the need for more permanent 'bench scientist' positions, comments that "the problem for universities of insecure funding from research grants is still there despite the new employment legislation." Nancy Rothwell adds that "UKLSC would like to see more financial resources being devolved to university departments to enable them to underwrite a limited number of permanent positions for contract research staff that may be financed on a rolling basis from grant income. At present it is difficult for smaller departments to do this".

Reasons to be reasonably cheerful

The CSR's measures to boost PhD stipends and training and to improve post-docs' salaries and career structure, along with measures afoot to put an end to the culture of short-term contracts, certainly were exigent. It comes as little surprise that many of the people I interviewed summarised these measures and changes as "very welcome".

Many, including Sir Gareth, Peter Cotgreave and Rodney Eastwood, add that the CSR has not just poured a considerable amount of money and initiative into the people dimension of

British science: it has also invested a great deal in much of the science base, from school labs and the recruitment of teachers, to university funding, capital and infrastructure. Rodney Eastwood concludes that "the result of all these changes ... can only be of benefit to all those who work in scientific research".

It is, however, just the start required to significantly reverse the decades of severe under-funding in British science. The IoB's Jonathan Cowie, supported by Peter Cotgreave, cautions that the CSR's spending announcements must be put into perspective: "Unfortunately, all the recent spending pronouncements relate to investment in the Science Base (which accounts for less than half of the total Governmental investment in UK Science). How Government Departments decide to invest in R&D will therefore determine whether the increased investment in the Science Base will have a chance of nurturing UK science's roots."

That may be so, but things are definitely looking up and there's some exciting momentum gathering.

And in the meantime, British bioscience PhD students and post-doc researchers will be in a slightly better position to toast to their much deserved and long overdue increased stipends and salaries, and promises of improved career training and structures. But easy does it – the increases don't come into effect for a few years yet.

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Physiological Control of Behaviour at Low Temperatures

In this article John Young discusses the relationship between severe low temperature and neuronal activity and goes on to suggest that an axonal equivalent to a warm overcoat may just be the key.



John Young

Temperature affects the rate of every physiological process. As low temperatures are experienced by animals from virtually all environments, animals that cannot regulate their body temperature – poikilotherms – must have mechanisms to survive low temperatures, and most of these survival mechanisms are well documented. Animals not only need to survive low temperatures, but some must also be able to produce rapid behaviours; they must have evolved compensation for the thermodynamic tendency of processes to slow down in the cold. These physiological adaptations that allow the production of rapid behaviours in poikilotherms living at low temperatures are less well understood. In my PhD I am investigating the function of the nervous system in marine crustaceans from temperate and polar environments.

Surviving low temperatures

Animals adopt different mechanisms to deal with low temperature depending on the duration of the cold period. Animals that experience low temperatures only transiently deal with the formation of potentially damaging ice crystals using mechanisms of *freeze tolerance*: nucleators control the formation of ice crystals in extracellular spaces, while cellular adaptations minimise cell shrinkage and ensure a rapid distribution of cryoprotectant compounds that lower the freezing point of body fluids. This enables freeze tolerant springtails (a six-legged hexapod), *Gomphiocephalus hodgsoni*, to survive temperatures as low as -38°C (Sinclair and Sjursen 2001; freeze tolerance reviewed by Storey and Storey 1996).

During the Antarctic summer, terrestrial species must be able to survive rapid

drops in temperature. The Antarctic springtail, *Cryptopygus antarcticus*, is able to survive rapid cooling over a 20h period from $+5$ to -5°C . This tolerance was originally believed to be the result of gut clearance, (thereby removing particles that could act as unwanted ice nucleators) and altering the concentration of body fluids, but Worland and Convey (2001) show that these mechanisms are not used.

Animals from permanently frozen environments use mechanisms of *freeze avoidance* to depress the point at which damaging ice crystals form in body fluids. Compounds that could act as ice nucleators are removed, polyols are accumulated and an external waterproofing prevents contact with environmental ice, the most potent of nucleators (reviewed by Zachariassen and Kristiansen 2000).

Maintaining behavioural activity

Animals that experience transient low temperatures generally show a reduction in behavioural activity and metabolic rate as temperature decreases. Over seasonal time scales they either become dormant, or continue to function normally with compensated physiological rates. Animals from high latitude or high altitude environments experience low temperatures permanently and therefore must remain active. The Alaskan beetle, *Pterostichus brevicornis*, shows normal behavioural activity at temperatures as low as -12°C , at which closely related temperate species could not survive (Baust 1972).

Maintained rates of behavioural output are believed to arise from the principle of *metabolic cold adaptation*:

which states that physiological rates should be equal in polar, temperate and tropical poikilotherms. An animal living in a low temperature environment is said to be cold-adapted if its metabolic rate is greater than that of a related temperate species cooled to the same temperature. The extent of cold adaptation depends on the extent of temperature fluctuations. There is little temperature compensation of metabolic processes in Antarctic marine invertebrates (e.g. Peck and Conway 2000), suggesting that aerobic capacity and energy expenditure is minimised and tuned to the stable marine environment. Whether terrestrial poikilotherms from permanently freezing environments show similarly low (uncompensated) metabolic rates, compared to related temperate species, is contentious. High rates of oxygen consumption between 5 and 10°C in a sub-Antarctic dipteran, *Paractora dreuxi*, suggest a rapid acceleration of metabolism as temperature rises after a cold spell (Crafford and Chown 1993), representing a metabolic adaptation to ensure maximum gains during periods of productivity. In contrast no evidence of metabolic cold adaptation was found in Arctic arthropods (Scholander *et al* 1953). This is believed simply to represent a cost-saving mechanism, allowing resources to be devoted to growth and development. The true story is confused because latitudinal differences in metabolic rates are prone to species-bias, and because of variations in the methodology used.

There are certainly mechanisms of cellular adaptation over seasonal and evolutionary time scales, but whether they aid compensated rates of physiological processes or simply allow survival is not known. It has been well documented that lipids become more solid with decreasing temperature, so to compensate, membrane fluidity is altered to maintain cellular function, with saturated fatty acid moieties substituted for their unsaturated equivalents (e.g. Clarke 1977).

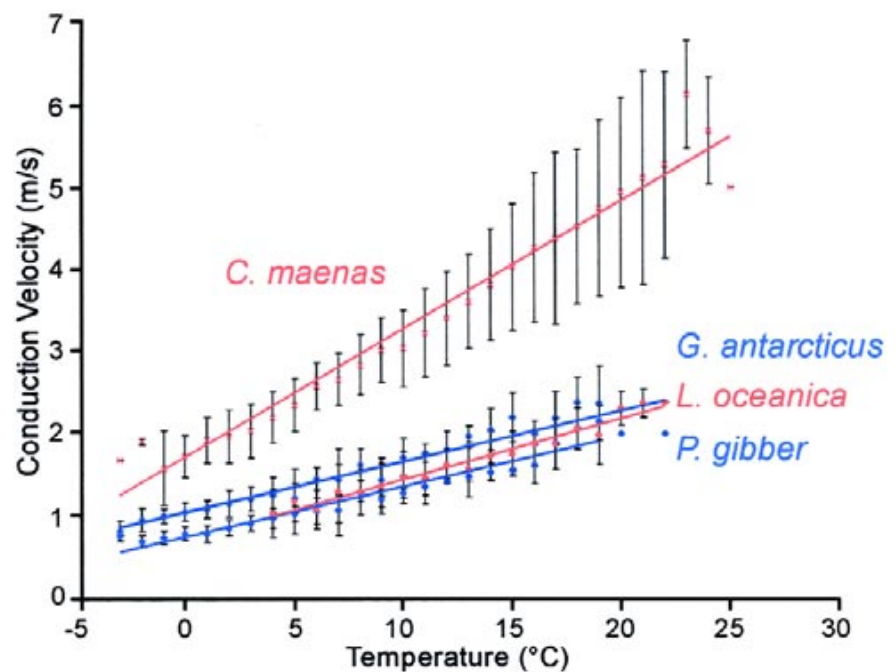


Figure 1 The temperature dependence of neuronal conduction velocity in the pereopodal nerves of four species of marine crustacea, with red denoting temperate species, and blue Antarctic species: *C. maenas* (4 experiments from 1 animal), *L. oceanica* (5 experiments from 1 animal), *G. antarcticus* (7 experiments from 4 animals) and *P. gibber* (4 experiments from 3 animals). For each species the mean conduction velocity and its 95% confidence interval are given at 1°C intervals.

Relating the viscosity of neuronal membranes to behavioural performance over a range of temperatures (e.g. Cossins *et al* 1977) led many to believe that it was key changes in fatty acid composition over seasonal or evolutionary time-scales that allowed some species to produce rapid behaviours at sub-zero temperatures.

Subsequent comparisons of closely related species from very different thermal environments have revealed other structural adaptations which permit occasional rapid behaviour in low temperature environments. In my PhD, I am assessing the effect of temperature on the neuronal control of behaviour in four marine crustacean species from very different thermal environments: the crab, *Carcinus maenas*, and the isopod, *Ligia oceanica*, from the British coastline, where the temperature varies between +2 and 24°C annually, and the giant isopod, *Glyptonotus antarcticus*, and the amphipod, *Paraceradocus gibber*, from Antarctica, where the sea temperature is $-1.8 \pm 1^\circ\text{C}$.

There were positive relationships

between temperature and neuronal conduction velocity in the leg nerves of all four species with propagation maintained up to 20°C (figure 1). This is particularly interesting as the Antarctic species do not survive temperatures above 6°C, supporting the hypothesis proposed by Prosser (1973) that other neuronal functions are more sensitive to temperature change than is axonal conduction. There is a difference between closely related species from different thermal environments, however; axonal conduction velocity was more rapid at any given temperature in *G. antarcticus* than in *L. oceanica* (ANCOVA $F_{1,139} = 29.52$, $p < 0.001$), suggesting some form of neuronal compensation.

A neuroanatomical basis for this finding was investigated using transmission electron microscopy of the same nerve. Although *L. oceanica* has a greater percentage of large (>20mm) axons than *G. antarcticus*, the large axons in the latter species had thick (5 µm) wrappings (figure 2). Experiments to determine the composition of these wrappings, and whether they increase

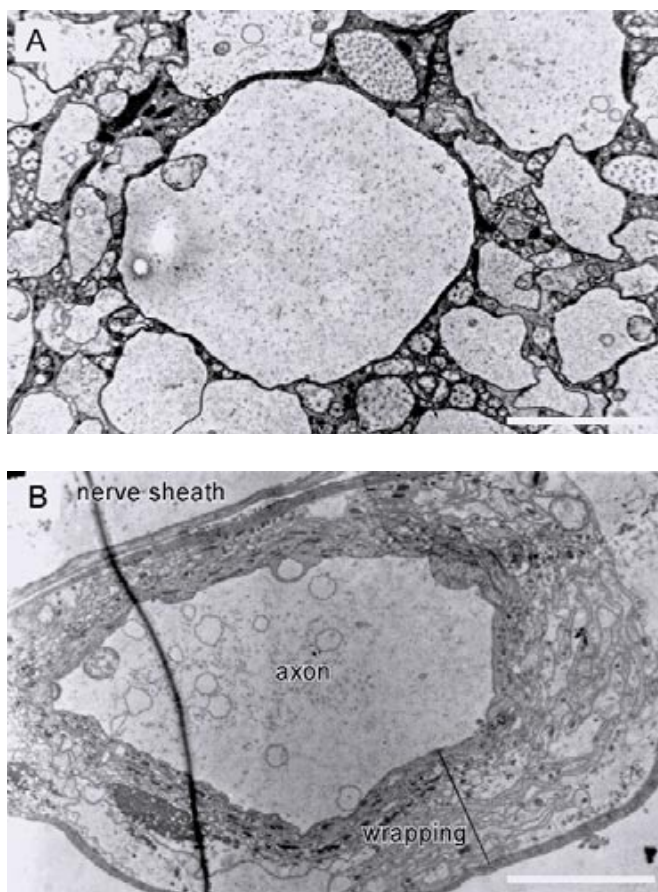


Figure 2 Transmission electron micrographs of transverse sections through the pereopod nerves of *G. antarcticus* and *L. oceanica*. Both scale bars are 5mm.

(A) Part of a *L. oceanica* nerve, showing large axons.

(B) A small *G. antarcticus* nerve, containing a single axon with a multi-layered wrapping.

The dark line is a crease in the section.

the speed of axonal conduction, are still to be performed.

The hypothesis that the wrapped axons of the Antarctic isopod, *G. antarcticus*, may serve to increase the speed of neuronal conduction, is supported by similar findings in other taxa. Alpine crickets (Morrissey and Edwards 1979; Edwards and Mann 1981) produce rapid bouts of walking over large distances at near-freezing temperatures along a surface of snow and ice. The closely related house cricket is torpid at the same temperature. This behavioural adaptation is explained by wrapped axons in the alpine species which are shown to continue propagating action potentials down to -3.5°C whereas axonal conduction ceases at $+4^{\circ}\text{C}$ in the house cricket.

There are few other examples of compensations that counteract the

tendency for motor functions to decrease in rate in low temperature environments. For many species that experience permanent low temperatures, particularly Antarctic marine invertebrates, reduced behavioural activity represents the most energy efficient way of coping with low food availability. These animals are unlikely to show neurophysiological compensation. The capacity to produce rapid behaviours may be reserved to a few species that either need to evade predation or scavenge for

food. Such species include a few Antarctic marine invertebrates, such as *G. antarcticus*, Antarctic marine vertebrates and alpine invertebrates. How the neurophysiological control of rapid behaviours is adapted for low temperatures is not known. Future experiments will determine what other adaptations allow rapid behaviour at both low and fluctuating temperature. Many questions remain, including what role does the nervous system play in governing the flexibility of an animal to tolerate changes in body temperature? Are the adaptations that allow rapid axonal conduction at low temperatures also responsible for the very narrow temperature range over which Antarctic invertebrates can produce coordinated behaviour?

By addressing these questions I hope that we can better our understanding

of the flexibility of the physiological control of behaviour of animals living in low temperature environments.

John S Young

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Acknowledgments

I thank Lloyd Peck, Keri-Lee Page and my supervisor Tom Matheson for their valuable comments on this manuscript. This work is supported by a studentship from the BBSRC. I would like to thank Professor Lloyd Peck from the BAS, and the National Science Foundation for the supply of animals.

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MRC and the 3Rs



Vicky Robinson

The MRC is committed to the principles of the 3Rs (replacement, reduction and refinement) and to ensuring high standards of care

for the animals that are used in the research it funds – currently approximately 20% of the research programmes funded by the MRC involve the use of animals. Recently, the MRC decided to take a more proactive role by inviting funding proposals for new work relevant to the 3Rs, and by establishing the Centre for Best Practice for Animals in Research (CBPAR).

MRC 3Rs funding scheme

MRC research programmes in areas such as antibody technology, imaging and the development of *in vitro* models already contribute to the development of non-animal methods or reduced animal use. In addition to this, the MRC is now inviting grant applications for research and/or the development of methods which are solely concerned with the 3Rs and laboratory animal welfare. The MRC has already awarded two strategic grants under the scheme. Dr Lars Sundstrom from the Department of Clinical Neurosciences at the University of Southampton has been awarded £200,000 (jointly funded with the Defence Science and Technology Laboratories) to develop and characterise a clinically relevant *in vitro* model of traumatic brain injury which mimics shear injury. Professor Paul Flecknell from the Comparative Biology Centre at University of Newcastle has been awarded £177,000 to identify and eval-

uate indicators of pain in rats of different strains and ages and following different procedures.

The MRC is keen to hear from any scientists who would like to discuss an outline proposal for research that is likely to make a significant contribution to the 3Rs. It would particularly welcome applications from multidisciplinary teams or proposals which would complement its increased investment in mouse genetics and physiology. All applications are peer reviewed. Anyone interested in discussing a research proposal should contact Dr Angela Williams (angela.williams@headoffice.mrc.ac.uk) or Dr Declan Mulkeen (declan.mulkeen@headoffice.mrc.ac.uk).

MRC Centre for Best Practice for Animals in Research

Working closely with scientists, vets, animal technicians, regulatory authorities and professional bodies, the CBPAR will be supporting the scientific community's commitment to the 3Rs by developing, promoting and implementing best practice guidance and expert advice on the 3Rs and laboratory animal welfare. The Centre will also be taking the lead on the ethical use of animals within MRC.

The CBPAR will be working proactively developing consensus best practice guidelines on husbandry and procedures, and reactively to address issues of concern. Currently the CBPAR is focussing on a range of issues including the care of primates used in scientific procedures, and with the other major funding bodies is developing welfare assessment schemes for genetically modified animals.

A key component of the CBPAR's work

will be the dissemination of information on the 3Rs. There is already a considerable amount of research carried out in the UK and worldwide on initiatives which will replace, reduce and refine animal use. The Centre will be disseminating the output of such work through a number of fora including its webpages, discussion groups and workshops. The CBPAR's webpages are currently under construction and should be complete by mid-Autumn (http://www.mrc.ac.uk/index/public_interest/public-ethics_and_best_practice/public-cbpar.htm).

Dr Vicky Robinson has recently been appointed to head the CBPAR. Vicky was formerly a scientist in the Division of Developmental Neurobiology at the MRC's National Institute for Medical Research, where she worked on the role of a family of receptor tyrosine kinases and their ligands in the patterning of the hindbrain and cranial neural crest. More recently, she worked in the RSPCA's Research Animals Department promoting the 3Rs in biotechnologies.

The CBPAR is in a nascent period and its detailed work plan will be presented to its Board of Management in October. Anyone who has any queries or suggestions for areas the CBPAR should be addressing should contact Vicky Robinson (vicky.robinson@headoffice.mrc.ac.uk).

Vicky Robinson
MRC

An update on The Journal of Physiology

I was elected Chair of the Editorial Board of *The Journal of Physiology* at the start of May 2002. My association with *The Journal* goes back over 15 years. I published some of my PhD work in *The Journal of Physiology* back in 1987 and soon afterwards found myself acting as a referee, supervised as I was by the then Chairman of the Board, Tony Edwards, and one of the Distributing Editors, Tim Rink. My load as a referee increased steadily over the years and I was invited to join the Board in 1997. I became a Distributing Editor at the start of 2001. On election as Chair I was immediately dropped in at the deep end since the Society had just initiated (at the suggestion of the Board) a tendering process for the contract to publish its journals. This process is still ongoing, but we now know it will result in a change of publisher from 1st January 2004. I therefore anticipate a busy period during my tenure.

Although there are likely to be major changes ahead for *The Journal*, a number of new features have been added over the past year. For a start, the format of the contents (that is the font and layout) changed from January. The change of font should hopefully keep all our online users happy as the PDF files are now much easier to read. This is something which has received criticism over the last few years and was basically a result of having a special hand-drawn Journal of Physiology font. The covers have also changed (at least the spines are noticeably different) with limited sectionalisation now on the back cover, after many years of discussion by the Board. Hopefully this will make content more accessible to readers. There are four very broad sections, Molecular and genomic physiology, Cell physiology, Tissue, system and organ physiology and Integrative physiology, covering all areas of physiology.

The introduction of the new online manuscript submission system last November went remarkably smoothly. After initial difficulties getting used to the new way of working, most people are now willing to admit that it does seem to operate very well. Although some of the personal contact with staff has been lost, this has been compensated for by the reduction in delays. The mean time from submission to acceptance is now the lowest ever, at just under 2.5 months. With the introduction of Physiology in Press, the publishing of copy-edited but not corrected articles online ahead of print, the delays from acceptance to publication are down to less than 1 month. This means that, on average, a paper can be published within about 3.25 months of submission. Rapid

Reports can now be published online within 2 months of submission. These times are a significant improvement, and one that *The Journal* is determined to maintain. Full publication statistics can be found in the Society's Annual Report.

The Journal of Physiology Symposia have continued to be a popular feature and the series continued in 2002. The first took place in Tübingen, Germany on 15th March on 'Normal and pathological excitation-contraction coupling in the heart', with the second shortly afterwards on 20th March in Los Angeles, California on 'Fetal programming: from gene to functional systems'. Plans are well advanced for a further symposium in 2003 on 'Ion channels: their structure, function and control' on 24th March in Fukuoka, Japan. To increase the attractiveness of the issue containing these symposium papers, *The Journal* also publishes associated papers, which undergo the usual reviewing process.

In January *The Journal* published its first 'Classical Perspectives' article to celebrate the 50th anniversary of the publication of the paper by Hodgkin and Huxley (117, 500-544 (1952)), which was the final paper in a series on voltage clamp experiments by Hodgkin, Huxley and Katz. This Perspectives article is accompanied online by the PDF file of the original paper. *The Journal* plans on having regular Classical Perspectives articles and so build up a collection of these classic papers, which hopefully will be interesting to regular readers but also a useful teaching aid for students.

Submissions to *The Journal* have increased in 2002 by about 7%. This increase is welcomed to ensure that *The Journal* continues to publish only the



Michael Ferenczi



Enrico Cherubini



David Attwell



Karl Gegenfurtner



Graham Lamb



Tomoyuki Takahashi

best papers. They continue to be handled by five Distributing Editors.

The Board has been joined this year by Michael Ferenczi, Enrico Cherubini, David Attwell, Karl Gegenfurtner, Graham Lamb and Tomoyuki Takahashi. We are also extremely grateful to Allen Cowley Jr who has kindly agreed to lead *The Journal's* new initiatives in the field of functional genomics and, with assistance from John Hanrahan and Richard Moss (our Topical Reviews Editor), to put together a special issue of *The Journal* for publication in January 2003.

The appointment of Jill Berriman as Managing Editor, to help to ensure that *The Journal* maintains its status as one of the leading physiological journals, has removed some of the duties of the Press Secretary. This post is currently vacant and is likely to be discontinued in the near future. Consideration is being given to creating a replacement position of Deputy Chair, a title which would more accurately reflect the duties concerned. The Board is considering ways to encourage the involvement of overseas Editors. The appointment of an International Deputy Chair has been suggested which would hopefully achieve this and increase submissions from overseas authors.

A number of Editors retired from the Board in July – Susan Wray (who had also served as Press Secretary), Michael Barish (a Distributing Editor), Stephen Lisney (Senior Ethical Editor), Ian Forsythe, George Stephenson and Wouter Wieling. Their contributions to the continuing development of *The Journal* have been invaluable.

Special thanks are also due to Barry Hirst for his long and dedicated service to *The Journal* as a Distributing Editor, Press Secretary and latterly as Chairman.

In my role as the new Chair I feel that *The Journal* must adapt rapidly if it is to benefit from the opportunities offered by electronic publication and avoid associated threats. I believe that better strategies must be devised for making *The Journal* more attractive to authors and for addressing the concomitant need to expand our readership. These are difficult goals to achieve but the efforts of a well-motivated Board should be sufficient to carry *The Journal* forward and I look forward to the years ahead.

Stewart Sage

Chair of the Editorial Board
The Journal of Physiology

Physiological Society International Workshop for Young Physiologists Current Directions in Exercise Physiology

As part of its International Relations programme of activities, the Society supported a Workshop for Young Physiologists in Zakopane, Poland from 14–17 April. Zakopane may seem an odd choice of location for such an activity as it is not recognised as a centre of excellence in physiology. It is best known as a winter sports resort, being located in the Tatra Mountains in southern Poland, close to the Czech border. As such, it enjoys excellent road and rail links with a large part of eastern Europe and the former Soviet Republics. It is also the location for an annual symposium in exercise physiology and sports medicine organised by the University of Krakow.

The decision to combine the young physiologist workshop with the Medicina Sportiva symposium had a number of attractions. It allowed the Society to participate in a well-organised event with an established reputation throughout eastern Europe. The Society was represented in Zakopane by David Brown (London) Ian Macdonald and Paul Greenhaff (Nottingham), Mike Rennie (Dundee) and Ron Maughan and Susan Shirreffs (Aberdeen). In addition, P-O Astrand (Stockholm), who is recognised as one of the founding fathers of the systematic study of human and exercise physiology, also participated in both the Symposium and the Workshop as a guest of the Society.



Top Ian MacDonald addressing the meeting.

Above Mike Rennie giving his talk (the morning after the banquet)

Below The local organisers (Zbigniew Szygula, centre, and Wojciech Gawronski, right) enjoying dinner with Erika Zemkova, a participant from Slovakia.





Top Per Astrand at the posters with Petra Alacova (Czech Republic) and Erika Zemkova (Slovakia).



Above David Brown (International Secretary) telling the Workshop organisers that it's too early in the day for students to be allowed to drink beer.

Below After a long hard day at the Workshop, the strain of speaking English begins to tell on one of the participants.

Bottom Mike Rennie puckering up for the Society



Most of the hard work involved in the organisation of the programme was carried out by local hosts Zbigniew Szygula and Wojtek Gavronski of the University of Krakow, in collaboration with David Brown. The workshop attracted a total of 28 young physiologists from across eastern Europe: there were representatives from Poland, Ukraine, Czech Republic, Hungary, Russia, Lithuania, Croatia, Slovakia, Belarus and Romania. The term "young" was interpreted rather more liberally than it might be in the UK, with the oldest of the students being 40. One applicant aged 72 was not accepted.

The programme began with an evening session including two plenary lectures (P-O Astrand and Ron Maughan) which were followed by a reception at which the usual Polish hospitality was in great evidence. Each of the following three days followed the same format, with lectures for Workshop participants and Symposium delegates in the mornings and separate sessions for the Workshop participants in the afternoons. In addition to the lectures from the Physiological Society representatives, this arrangement allowed the students to hear the other Symposium speakers.

For the afternoon workshops, students were split into three groups and rotated around the three sessions. Two were discussion sessions where the participants had an opportunity to discuss their research projects and other issues of topical interest, and one was a hands-on lab-based session. The lab session was run by Hanna Kaciuba-Uscilko, Kristina Nazar and Andrew Ziemba of the Polish Medical Research Council research laboratories in Warsaw. After a slow start during which the students gradually became accustomed to the informal style of postgraduate discussions favoured by the UK representatives (and to their use of English), a useful interchange of ideas developed. The process was greatly assisted by the hospitality of our Polish hosts, who ensured that there was

ample opportunity for informal discussions in a convivial atmosphere.

During the Medicina Sportiva Symposia there is always a competition for the best poster presentation, and participants in the Young Physiologists programme were encouraged to submit their posters for this competition. Most of the poster presentations, including all of those submitted by the Workshop participants, were in English, and a wide range of research topics were presented. It is an indication of the high standard of the presentations made by the Workshop participants that two of these posters won prizes, even though the competition was open to all participants in the Symposium as well as the Workshop, and attracted a total of 58 posters.

First prize was awarded to Ales Jacubec and Petra Alacova from the Czech Republic, whose poster was entitled "Spectral analysis of heart rate variability during long term recovery after dynamic exercise".

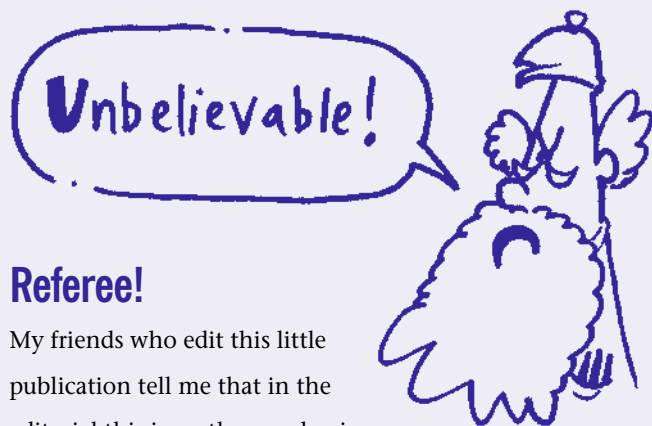
The third prize was awarded to Andrew Vlasov and Petr Kvashuk from Russia for their poster entitled "Central nervous system activity and physical work capacity in elite athletes".

Another of the posters was awarded a commendation: "Contraction force, fatigue and recovery of quadriceps muscle after leg immobilisation" by Alma Kajeniene and Rona Baceviciene from Lithuania.

The work of the Society in sponsoring and supporting the programme was much appreciated by all of the participants and several have followed up with enquiries about opportunities for postgraduate study in the UK, as well as with questions about opportunities for participating in the Scientific Meetings of the Society in the UK. If these enquiries translate into positive actions, then the workshop will be judged a success.

Ron Maughan

University of Aberdeen



Referee!

My friends who edit this little publication tell me that in the editorial this issue they are having a dig at the anonymous referee-ing system.

To which I say: Good on yer boys.

Because you can't work in science for very long without getting on the wrong end of anonymous referee-ing at least once. Or, more accurately, practically every time you submit something.

And it tends to get you very hot under the collar.

Not so much with papers – those you can always send somewhere else. After all, there are plenty of journals. But grants – that's a different story. Although there are sometimes second chances, and these days even rights of response, the relative scarcity of biomedical funding, the one-in-five or whatever success rate, and the pressure from the bosses to "show us the money" makes it a fraught business. To paraphrase Bill Shankly: "A matter of life and death? It's much more important than that."

So when, following the rejection of your grant, you get some referee's comments clearly written by someone who was:

- (i) too busy to actually read the grant very carefully;
- (ii) largely ignorant about the background or subject matter;
- (iii) nonetheless happy to trash it:

Well, if you don't know, take it from me: it makes you SERIOUSLY *!#!Y CROSS.

Has nobody ever explained to these people that their comments are supposed to deal with the scientific matter of the specific proposal in front of them?

Perhaps they just find such a remit too creatively restrictive.

Anyway, you discover early on that the anonymous referees of your grants like to air their opinions. Even if "toxic gases" comes closer to the truth than "air".

A few examples to make the point.

From my own collection, I recall particularly a review that only devoted one sentence to the actual science in the grant proposal, which it said was alright. Instead, it spent half a

page attacking the conclusions in a paper I had published on a related, but not directly relevant, subject. Hmm, must have annoyed that person somehow.

Needless to say, I didn't get the grant.

Or let's take a friend of mine – we'll call him Dr Grantless – who applied for a grant on his pet problem, the workings of the J-type cells of the organ of Q. He had been working on these J-type cells for twenty-odd years, publishing several dozen respectable papers in decent journals. The referee commented: "Dr Grantless proposes to examine some aspects of the physiology of the J-type cells. There are three UK centres for J-cell research. These are X-ford, Y-chester and Z-burgh."

Oops. Unfortunately for my friend, he was working at the University of W-field.

He didn't get the grant either.

I could go on. Believe me. Have you ever read any of the following phrases (all real examples contributed by various colleagues, I hasten to add)?

"The applicant has only a modest reputation", "...his/her work has so far not resulted in any major advance...", "...the applicant's publications are invariably in low-impact journals..."

The point is that all the people who wrote these frankly unscientific – ridiculous? – things, were protected by the anonymous referee system.

Would they have written stuff this casually damning, not to say prejudiced, if they had had to sign their names?

Perhaps – and admittedly it's only a chance – they might instead have had to try and think of some comments dealing with the scientific matter of the grants they were reviewing.

As the editor of a journal I know where the referees do have to sign their reports once wrote: "Signed reports haven't meant less scientific rigour. But they have meant less invective."

From which one might infer that doing away with anonymity for referees altogether, for both grants and papers, would be a good thing.

To coin a phrase:

You might well think that;

I couldn't possibly comment.

Oh. Except maybe anonymously.

Mark Cain

Report of the House of Lords Select Committee on animals in scientific procedures

In March 2001, the House of Lords appointed a Select Committee to conduct an enquiry into the use of animals in scientific procedures. The Committee received over 350 written submissions, and took evidence from over 40 individuals and organisations, including the Physiological Society's President Colin Blakemore, the Chief Executive of the RDS Mark Matfield, and the Chairman of the UKLSC Nancy Rothwell. Representatives from anti-vivisection organisations such as the BUAV and NAVS were also heard alongside Home Office and Department for Health representatives, and those from the APC. The report was finally published on the 16th July 2002.

The Lords concluded that animal experimentation is currently necessary both for applied research and for research aimed to increase knowledge. The Report also included many suggestions regarding the increase in research into 'alternatives', and the streamlining of bureaucracy.

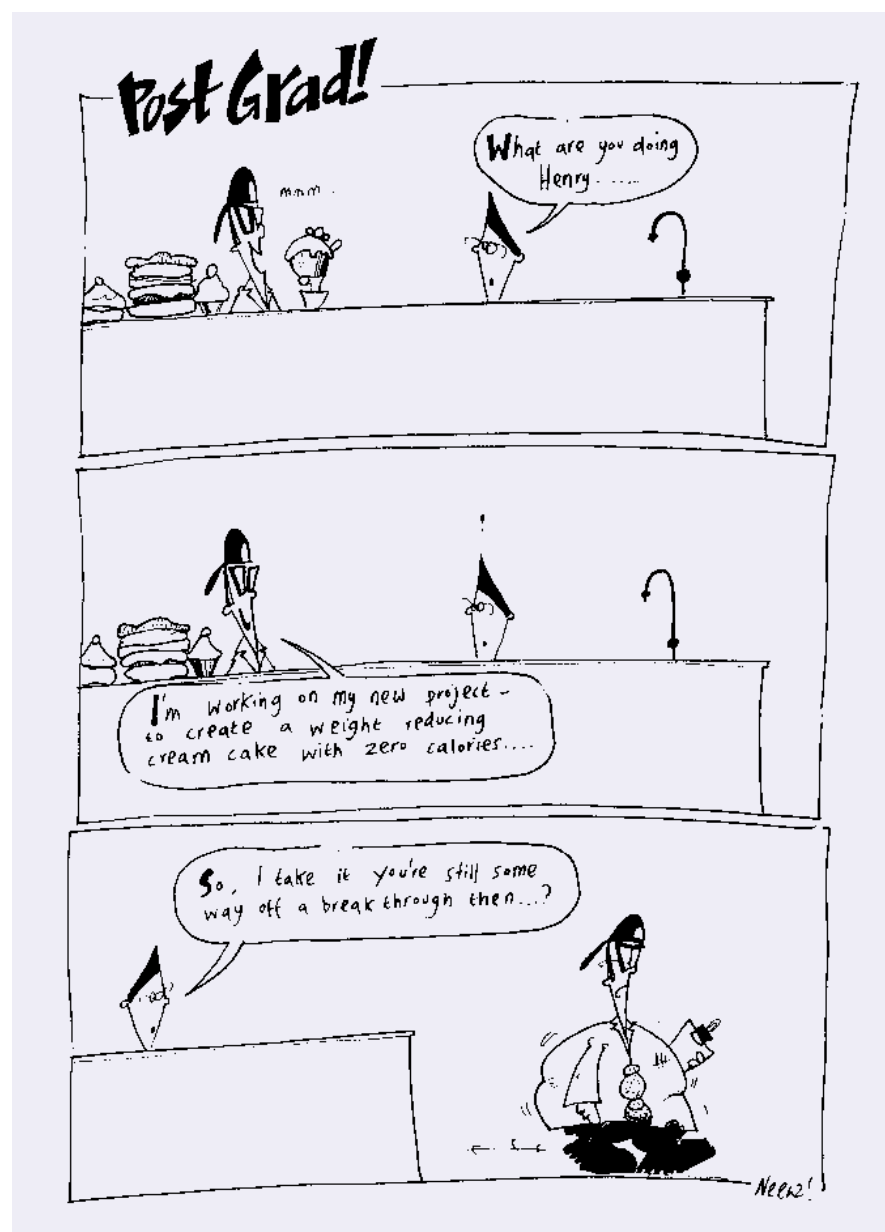
The Physiological Society plays an active part in the UKLSC Animal Science Group, which met to discuss the Report at the beginning of August. Under the temporary chairmanship of Professor Bruce Matthews (the Physiological Society's representative), the Group agreed it would be useful to comment on the Report, and that those comments should be sent to all Members of the House of Lords with an interest in science, prior to the ensuing debate.

The Group agreed that the Report should be broadly welcomed for its clear support for the need of animal experimentation. In addition, many of the conclusions and recommendations were useful and a good basis for debate. Specifically, the Group agreed with many suggestions regarding research

into replacement and refinement, and will suggest that the new MRC Centre for Best Practice should take a lead on this (Dr Vicky Robinson, the Centre's new Head, was present at the meeting and agreed with this proposal). In addition, the Group strongly supported recommendations regarding the simplification of the licence application procedure, although will comment that the suggested target of reducing the length of the application is not the only issue.

Two particular areas where it was felt that further discussion would be useful were comments regarding the Animal Procedures Committee (APC) and the suggested periodic review of the Home

Office. Whilst the Group agreed that strengthening the Secretariat of the APC would be useful, it was felt that the current composition of the Committee was a cause for concern in extending its jurisdiction, for instance to instigate a review of Home Office regulators. It was felt that while periodic review might be useful, to increase consistency and share best practice, it should be undertaken by a body with no interest in the outcome. It will be suggested that the National Audit Office might be more appropriate, and that reviews would need to be against a set of criteria which should be determined after consultation with the major stakeholders.



The Group will also suggest that the proposed relaxation on the use of terminally anaesthetised animals for training surgeons should be extended to include training scientists. It was felt that this would ultimately result in less animal suffering, as scientists would become more adept more quickly than is possible by current methods of training using demonstrations and observation of experienced staff.

These are only a selection of the comments made by the group and forwarded to the Lords. A full report of all the recommendations made can be viewed at <http://www.uklsc.org/asg/default.htm>, and the House of Lords Report can be downloaded or purchased from <http://www.publications.parliament.uk/pa/ld/ldanimal.htm>.

Maggie Leggett

New grant scheme for affiliate members

The Physiological Society has set up a new grant scheme to help UK based Affiliate Members attend Home Meetings of the Physiological Society. The Society has become increasingly aware that whilst Affiliates are applying for funds to attend and present at meetings overseas, the cost of attending UK meetings deters them from attending national Physiological Society meetings. Previously there were funds made available to attend these meetings via the Young Physiologist Guest Scheme; however, Affiliates were prevented from applying on their own behalf and were forced to submit applications via their supervisor. We are therefore trialling a new scheme, where any Affiliate member who is planning to attend and present at a meeting can apply for a bursary to cover their travel, accommodation and the Society dinner. Currently, this scheme will run alongside all other existing schemes, and will then be reviewed next year. The scheme will first be in operation for the UCL meeting.

Criteria for eligibility to the new scheme would be:

- 1 Affiliate membership
- 2 Oral communication/poster presentation as first author at the meeting

An Affiliate would be eligible for one Home Meeting Award per annum, and cannot apply under any other scheme (e.g. Young Physiologist Guest Scheme or International Bursary) to attend the same meeting. All Affiliate Members were emailed about the scheme in good time to apply for a grant for the UCL Meeting, and application forms are available on the website <http://www.physoc.org/Grants/>. We will be reviewing the scheme in 2003. All grant enquiries should be directed to Jamie Gould, at jgould@physoc.org.

Maggie Leggett

Change in policy for *The Journal of Physiology* and *Experimental Physiology* from January 2003

From January 2003, all journal titles in the reference lists in both *The Journal of Physiology* and *Experimental Physiology* will be in the abbreviated form. Punctuation is also changing at the same time so in future all submitted manuscripts should list references in the following style:

Lipp P, Egger M & Niggli E (2002). Spatial characteristics of sarcoplasmic reticulum Ca^{2+} release events triggered by L-type Ca^{2+} current and Na^{+} current in guinea-pig cardiac myocytes. *J Physiol* 542, 383-393.

Cividjian A, Rentero N, McAllen R & Quintin L (2002). A simple method for generating a blood pressure-unit activity relationship for central cardiovascular neurons in the rat. *Exp Physiol* 87.5, 535-538.

We hope this will be a welcome change for authors.

Frontiers of Physiological Research A Physiological Society Teaching Symposium

University of Liverpool
Wednesday 4th December 2002

Programme

9.30 – 10.15 Coffee

10.15 – 10.45

Dr Alan Morgan (Liverpool)
Regulation of exocytosis by protein phosphorylation

10.45 – 11.30

Professor David Eisner (Manchester)
Calcium and the heart: the good and the bad

11.30 – 12.15

Professor Mark Dunne (Sheffield)
Ions, genes and defects in Insulin

12.15 – 13.00

Professor Deborah Withington (Leeds)
Using auditory neuroscience to save lives

13.00 – 14.00 Lunch

14.00 – 15.00

****Special guest lecturer****
Professor Kathleen Morgan (Boston)
Why Calponin is essential for smooth muscle function

15.00 – 15.30

Professor John Quinn (Liverpool)
Utilising the human genome DNA sequence information to fight disease

15.30 – 15.50 Tea

15.50 – 16.20

Dr Michael White (Liverpool)
Imaging of signalling, transcription and cell fate in single living mammalian cells

16.20 -16.50

Professor Paul Trayhurn (Liverpool)
Nutrition – An Integrative Science at the Frontiers of Biomedicine

17.00 Refreshments

THE JOURNAL OF PHYSIOLOGY

SYMPOSIUM

For further information
go to

www.jphysiol.org

or email

jpsymposium@physoc.org

Ion channels: their structure, function and control

*at the joint annual scientific session
of the Japanese Physiological and
Pharmacological Societies*

Monday, 24 March 2003
Fukuoka, Japan

Organisers: **Yoshihisa Kurachi** and **R. Alan North**

Speakers:

R. Alan North

Sheffield, UK

ATP-gated ion channels

Eric Gouaux

New York, NY, USA

Structure and function of
ionotropic glutamate receptors

Yoshinori Fujiyoshi

Kyoto, Japan

Structure and function of ion
and water channel molecules

Francisco Bezanilla

Los Angeles, CA, USA

Activation gating of voltage-
dependent ion channels

Lily Yeh Jan

San Francisco, CA, USA

Expression and sorting of ion
channels

John P. Adelman

Portland, OR, USA

Control of channel gating by
intracellular substances

Yoshihisa Kurachi

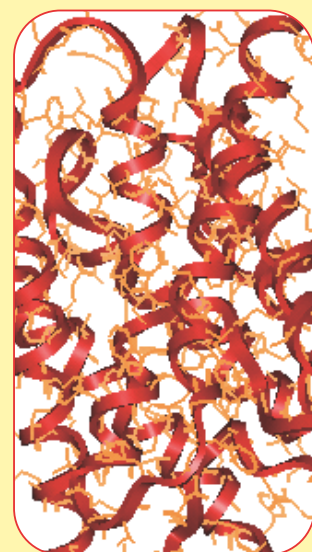
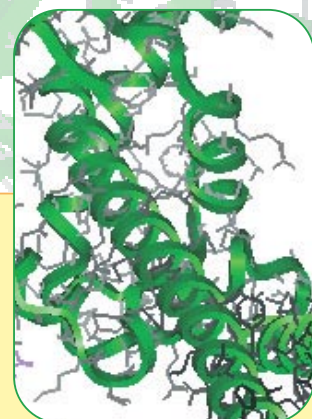
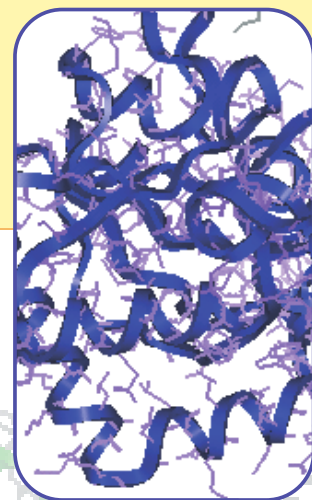
Osaka, Japan

Cell-signal control of channel
function and localization

Susumu Seino

Chiba, Japan

Gene-targeting approach for
channel function (knock-out
mice of Kir6.1 and Kir6.2)



The Physiological Society

APPLICATION FOR INTERCALATED BSc BURSARY

(PLEASE TYPE)

Applicant's details

Name	Date of Birth	
Address		
	Postcode	
Tel	Fax	Email

Desired Course of Study

Institution where intercalated course will take place (name and address)

Details of physiology element in course (must include experimental physiology project).
Please attach a one page summary of the experimental project, with title and supervisor

Funding bodies to whom application for fees, subsistence etc have already been made

Please supply additional information or comments concerning your efforts to obtain funding from another source (use continuation sheet if necessary)

Career Objectives

Reasons for wishing to intercalate a BSc, including any relevant background, accomplishments to date and career objectives (use continuation sheet if insufficient space)

Previous Studies and Relevant Work Experience

A Levels/Highers	Subject	Year	Grade
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A Levels/Highers	Subject	Year	Grade
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A Levels/Highers	Subject	Year	Grade
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A Levels/Highers	Subject	Year	Grade
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University Degree Subject

Institution

Course subjects/grades	
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Year 1

Year 2

Year 3

<p>Details of any special projects/outstanding achievements</p>

Other relevant work or study prior to present course

Confidential Letters of Support

The application must be accompanied by letters in support from two referees. These will normally be the Head of Department or Dean of the Institution in which you wish to take an Intercalated BSc, and an academic tutor who knows your work and personal circumstances, including financial.

1 Name	Position
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1 Name	Position
--------	----------

Address _____

Tel

2 Name	Position
--------	----------

2 Name	Position
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Address _____

Tel

If you are awarded a grant, we would like to transfer the funds directly into your bank/building society account. Please complete. (All information is confidential)

Bank/Building Society	Account Number
-----------------------	----------------

Bank/Building Society	Account Number
-----------------------	----------------

Name of account holder	Sort Code
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Name of account holder	Sort Code
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On completion, the first referee should return **SIX COPIES** of this form and of supporting documentation to The Administrator (BSc Bursaries), The Physiological Society, PO Box 11319, London WC1V 6YB.

Closing date November 30th.

9th BOC Priestley Conference

INSPIRED GASES: THEIR MEDICAL USES

The Royal College of Physicians, London, UK

14 - 16 January 2003

Introduction

The conference is the ninth in a highly respected series which celebrates the importance of gases and their chemistry to the health and wealth of the nation, and includes cutting-edge research and a schools competition. This conference addresses the role that gases play in enhancing medical diagnosis and therapy. In particular, various imaging techniques, respiratory function and surgical methods will be discussed. This event is being held at The Royal College of Physicians by kind permission of the Treasurer.

This event, Code Number A252, has been approved for External credit for the CPD Scheme of the Federation of Royal Colleges of Physicians in the UK and by The Senate of Surgery of Great Britain and Ireland.

Talks will include:

- **Structural and Functional Lung MRI using Hyperpolarised Noble Gases**
- **Carbogen - Imaging and Treatment**
- **Microbubbles: Contrast Agents for Ultrasound**
- **Carbogen Informs on Tumour Microvessel Function**
- **Lung Function Gases - Future Directions**
- **PET Scanning**
- **Heliox and PICU**
- **Space: The Medical Challenges**
- **Supplemental Perioperative Oxygen**
- **Heliox and Symptom Control**
- **The Long and Short of Oxygen Therapy**
- **Cryosurgery - Ar, N₂O, N₂ & CO₂**
- **Gases in Diving**

Further Information

For further information, please contact: Penelope Mohamed
9th BOC Priestley Conference, Royal Society of Chemistry
Scientific Affairs and Conferences, Burlington House, Piccadilly
London W1J 0BA UK tel: +44 (0) 207 437 8656 fax: +44 (0) 207 734 1227
email: conferences@rsc.org

web site: www.rsc.org/lap/confs/9boc.htm

RS•C
ROYAL SOCIETY OF CHEMISTRY

Noticeboard

No notice is carried for more than three successive editions. Notices are starred so that readers can see at a glance whether this is the first (one star) or final (three stars) appearance of the notice. Notices for the Spring 2003 edition should reach the **Administration Office by 4 January 2003.**

Please note that while members are welcome to advertise relevant events in the Magazine and on the website, advertisements via email will be restricted to events sponsored by the Society.

YOUNG PHYSIOLOGISTS' SYMPOSIA 2002

Prospective bids to hold symposia in 2003 should in the first instance be forwarded to Maggie Leggett at mleggett@physoc.org.

YOUNG PHYSIOLOGISTS' SYMPOSIA 2002

UCL

Monday 19th December

'The 'Ins', 'Outs' and 'In-Betweens': Nerve Cell Communication'

The Society will cover accommodation and dinner for those attending and presenting at the Symposium.

Main contacts:

Alison Foster, a.foster@ucl.ac.uk

Stephanie Parsley, s.parsley@ucl.ac.uk

CAREERS CONFERENCES

Organised in conjunction with other UKLSC Societies, these are suitable for undergraduates and postgraduates. There will be talks on a variety of careers, from patent law to science journalism and working in industry, and an opportunity to have your CV reviewed by a specialist. The final conference of the year will be held at:

King's College, London

30 November 2002

It is still possible to register for this conference.

TEACHING SYMPOSIUM

University of Liverpool

4 December 2002

This symposium brings together some leading physiologists, and will interest undergraduates, postgraduates and Members. Registration for this one day meeting will be absolutely free. Further details are available on the website.

MOLECULAR TECHNIQUES FOR LIFE SCIENCES

Glasgow Caledonian University
27-31 January 2003

This is a hands-on laboratory based course to introduce participants to techniques used in molecular biology investigations by a sequential experimental programme and intercalated lectures to transform tissue to sequence. Details can be accessed from our website www.sbbs.gcal.ac.uk/ short courses or by contacting Adrian R Pierotti at the following address:

School of Biological & Biomedical Sciences
Caledonian University
Glasgow G4 0BA
Scotland

Phone: +44 (0)141 331 3241

Fax: +44 (0)141 331 3208

http://sbbs.gcal.ac.uk/research/staff_profiles/Adrian_Pierotti.html

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LTSN BIOSCIENCE AUTUMN 2002 PROFESSIONAL DEVELOPMENT PROGRAMME

Programme of events:

Birmingham

23rd October 2002

LTSN Bioscience Professional Development Programme:
Diversifying Assessment for Effective Student Learning

Leeds

7th November 2002

LTSN Bioscience Professional Development Programme:
Personal Transferable Skills and Practical Work – problems and Strategies

Newcastle

28th November 2002

LTSN Bioscience Professional Development Programme:
Exploring Tools for On-line Assessment – a whistlestop tour for busy academics

Registration for all events is free of charge. Further details can be obtained from: <http://bio.ltsn.ac.uk/events/futureLTSNfeed.htm>

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40th SPRING MEETING OF THE BRITISH MICROCIRCULATION SOCIETY

Bristol
7-8th April 2003

The meeting includes a symposium on Lymphatic Research

UK Organiser: Dr Dave Bates

Further details can be obtained from:

BMS Secretary
Microvascular Research Laboratories
Department of Physiology
University of Bristol
Southwell Street
Bristol BS2 8EJ

Tel 0117 928 9818

Fax 0117 928 8151

email: Dave.Bates@bris.ac.uk

www.microcirculation.org.uk

Abstract and registration deadline
7th March 2003

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