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# The Physiological Society Magazine

*Sheffield Meeting*

Features on:

*New Governance proposals – the results*

*Mammalian two-pore potassium channels*

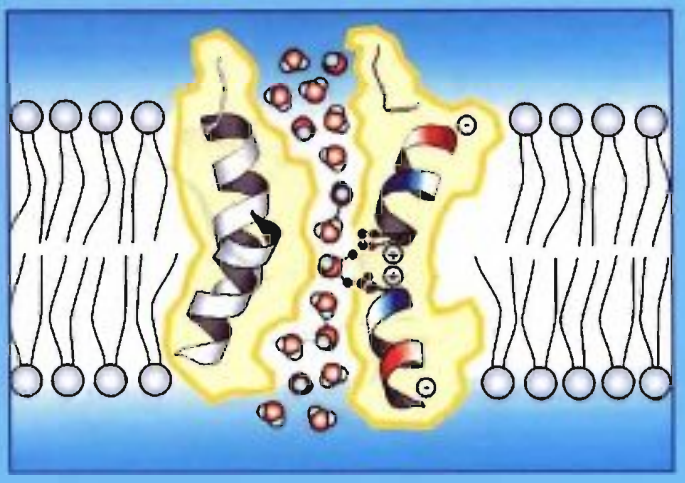
*Molecular determinants of the M-current*

*The importance of pH homeostasis and its correct nomenclature to physiology*

*Can gases cross biological membranes through channels?*

*Hypoglycaemia and central white matter*

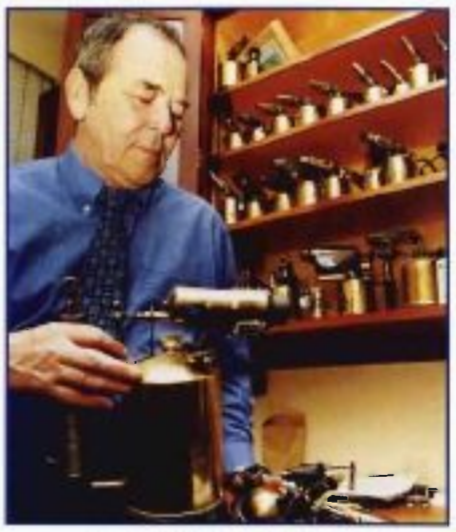
*Talking to the Press*



**Summer 2001**

**No 43**

*Peter Andrews (Chairman of Department)*



*Ivan Dart (with his collection)*

*Exterior of Department of Biomedical Science*

*Mark Dunne's Group: (back row, left to right) Karen Cosgrove, Anne Lee, Philippa Barnes, Rachel O'Brien, (middle row) Anne-Marie Gonzalez, Kate Hinchcliffe, Ruth Shepherd, (front) Mark Dunne*

*David Grundy's Group: Standing (left to right) Alan Brunsden, Charlotte Booth, Tony Kirkup, Mario Müller, (seated) Pauline Turner (Editorial Assistant for Neurogastroenterology), David Grundy*

*Front cover: Diagram of Aquaporin 1, reproduced by kind permission from Nature, Murata et al. Nature (2000) 407: 599-605.*

# Contents





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## ACTION POINTS

**Affiliate Travel Grant Scheme:** The next deadlines for receipt of applications are 31 May, 31July and 30 September 2001.

**MSc Bursaries:** The next deadline for receipt of applications is 31 May 2001.

**BSc Intercalated Bursaries:** The next deadline for receipt of applications is 30 June 2001.

**Postgraduate Support Fund:** The next deadline for receipt of applications is 31 July 2001.

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**Bristol Meeting (5-7 September 2001):** Abstracts must be submitted to the Meetings Secretary's Office by 7 June 2001.

**York Meeting (17-19 December 2001):** Abstracts must be submitted to the Meetings Secretary's Office by 20 September 2001.

**Address for abstract submissions:** The Meetings Secretary, The Physiological Society (Abstract Submission), Dept of Biomedical Science, The University of Sheffield, Western Bank, Sheffield S10 2TN

**Magazine:** Letters and articles and all other contributions for inclusion in the Summer issue should reach the Administration Office by 7 May 2001. Please cite all references in articles in the style of The Journal of Physiology.


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## GUIDELINES FOR CONTRIBUTORS

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### 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

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

### 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 Editor, to the Editorial Assistant or to a member of the Magazine Editorial Group (see below).

### Magazine Online

The magazine is now available on our website.

# WELCOME TO THE UNIVERSITY OF SHEFFIELD

## BIOMEDICAL SCIENCE IN SHEFFIELD

Biomedical Science represents the application of biology to medical problems. From its origins in Anatomy and Physiology, the research of this Department is focused not only on the ways in which macromolecules are organised to form functioning cells, and how those cells then interact to form tissues and ultimately develop into a whole organism, but also on the direct investigation of human disease processes and their treatment. Recent progress in molecular genetics, culminating in the 'Genome Project', is laying bare the 'nuts and bolts' of living organisms. The challenge for the foreseeable future is to understand the mechanisms by which those molecular nuts and bolts are integrated at progressively higher levels of organisation. Already, that understanding is providing new insights into human disease processes and new approaches to disease prevention and cure.

The Department of Biomedical Science has continued to evolve since the Physiological Society last came to Sheffield, in 1996. Since that time new developments in biology and a considerable number of new appointments have markedly changed the research focus of the Department. Signal events were the appointment of Professor Philip Ingham in 1996 to head a new Centre for Developmental Genetics, and the appointment of Professor Alan North in 1998 to head a new Institute of Molecular Physiology.

The Centre for Developmental Genetics represented a new departure for the University, and has now grown to encompass some 9 academic staff with major research programs ranging from the study of fruit flies and zebra fish, to study of mouse development and the use of embryonic stem cells. This includes my own research areas, which are concerned with the use of human embryonal carcinoma (EC) cell lines, and more recently human embryonic stem (ES) cell lines to investigate the regulation of embryonic cell differentiation in a way pertinent to human development. As in many other Universities, modern developmental biology has become the successor to the more traditional discipline of anatomy. Molecular Physiology, on the other hand, represents a more continuous development. The new Institute has built upon and greatly extended the existing strengths in the Department in electrophysiology, focusing on the biology of ion channels and cell signalling mechanisms. As a consequence of these new developments, the Department was recently awarded, together with our neighbouring Department of Molecular Biology and Biotechnology, a JIF grant of £23 million and a Wolfson Foundation grant of £3 million to undertake a major refurbishment of the Western Bank Complex that houses our two departments. In addition to refurbishment of the existing laboratories, new transgenic mouse facilities will be created, and a new building to house the Institute of Molecular Physiology will be constructed. Work is expected to begin during the coming summer.

### Aspects of Research in the Department of Biomedical Science

The Institute of Molecular Physiology was established in the University of Sheffield in 1998. The current academic staff members of the Institute are Professors Alan North, Annmarie Surprenant, Mark Dunne and Matthew Holley: the University has committed four further posts for which recruitment is currently on-going. It is anticipated therefore that the laboratory staff of about 30 (research associates, research assistants, postgraduate students) will double as recruitment proceeds. The Institute will be accommodated in a new building that is to be constructed on the east side of the Firth Court quadrangle. Research in the Institute is particularly focussed on the contributions to cell physiology of membrane proteins that function as receptors and ion channels; there is a particular emphasis on those molecules known or hypothesized to be associated with human disease. Major interests of Alan North, and Annmarie Surprenant at present are the elucidation of the structure and function

of the P2X family of ATP-gated ion channels in nerve cells and macrophages. Mark Dunne's research group is investigating the molecular mechanisms of ß-cell defects that are associated with the $K_{ATP}$ channelopathy Hyperinsulinism of Infancy (HI), and the development of human insulin-secreting cell lines for HI and diabetes therapy. Matthew Holley has research interests that include the mechanisms of development and regeneration in auditory and vestibular sensory epithelia within the mammalian inner ear. In this way he forms one of a number of links through to the Developmental Biology Centre, in which Tanya Whitfield is using the Zebra fish model to investigate the genetics of ear development. The main technologies represented within the Institute are molecular biology, patch-clamp electrophysiology (native dissociated cells, heterologously transfected cells, brain slices), protein purification and expression, cell biology and cell imaging techniques including confocal microscopy.

*Annmarie Surprenant's group: (left to right) Xuenong Bo, Miran Kim, Hari Chirakkal, Claire Fenech, Heather Wilson, Jayne Bailey*

In the Department of Biomedical Science, physiology-based research includes gastro-intestinal and epithelial transport and neuroscience. The group of Jackie Hardcastle and Peter Hardcastle are concerned with the mechanisms of intestinal transport and their regulation in health and disease, with particular emphasis on the abnormalities that occur in cystic fibrosis. In collaboration with Chris Taylor at the Children's Hospital in Sheffield they are using both intestinal biopsies from human patients and tissues from transgenic cystic fibrosis mice to examine the transport defects that contribute to the symptoms of the disease and to test the effects of possible therapeutic agents.

*Annmarie Surprenant's group: (left to right) Elena Adinolfi, Valeria Spelta, Alison Grainge*

Research on sensory signal transduction from the gastrointestinal tract is conducted by David Grundy's group. *In vitro* and *in vivo* approaches to visceral afferent sensitivity are conducted with a particular emphasis on mediators released from mast cells, endothelium and enteroendocrine cells in transmitting sensory information from the intestinal lumen. The group in Sheffield interacts closely with another in Tübingen, Germany, where David Grundy is a Gastprofessor. Collectively they are studying how inflammation alters afferent sensitivity and brainstem processing of sensory signals from the gut. The editorial office of "Neurogastroenterology and Motility", the official journal of the American and European Societies of Neurogastroenterology, is run from Sheffield by David.

Research in cellular and molecular approaches to renal physiology continues to develop at Sheffield, with a strong emphasis on potassium channels and mechanisms of their regulation. Louise Robson continues her work on cell volume regulation and, together with Jon Kibble and Stan White, new initiatives on the function of

*Jackie and Peter Hardcastle*

IsK in regulating $K^+$ efflux mechanisms and the role of twin-pore $K^+$ channels in renal function are also underway. Jon's expertise in *in vivo*

*Stan White's Group: (left to right) Stan White, Louise Robson, Charlotte Hill, Jon Kilbbie, Ian Millar, Andrew Neal, Judith Hartley*

approaches to mouse renal physiology forms a central pillar in work on the role of CFTR and other ABC proteins in renal function. Stan White's interest in secretory $K^+$ potassium channels of the distal nephron continues to evolve now concentrating on mechanisms of targeting of these proteins and identifying interacting protein partners.

## Teaching in the Department of Biomedical Science

Teaching, as well as research, is taken very seriously by the Department, and we were pleased to be awarded 24 points in our recent QAA visit. Indeed, each of the three departments (Biomedical Science, Molecular Biology and Biotechnology, and Animal and Plant Science) comprising the School of Biology in Sheffield was awarded 24 points. Nevertheless, teaching has also continued to evolve, and the Department is soon to embark on a new venture of 4 year degree courses. At the moment we recognise that many of our students do not intend to follow strictly subject based careers, while within the confines of a traditional 3 year course we believe it is difficult to provide adequate training of those who expect to go on to a researched based career. Therefore, we have decided to introduce the option of students following a three year course leading to a BSc., or a four year program leading to a masters qualification. Under this scheme, all our students will follow a common course structure in their first two years, branching out into themes related to the three core degree courses of Physiology, Anatomy and Cell Biology and Neuroscience in their third year, when a more general course leading to a qualification in Biomedical Science can also be followed. The fourth year will be largely devoted to an extended research project undertaken in the laboratories of one of our research groups, supplemented by additional course work that will include issues related to research ethics and the public understanding of science. We hope that the new scheme will enable us to meet the diverse needs of students in a more comprehensive manner. Of course, in addition to our science students, we also continue to teach anatomy and physiology to medical and dental students. Our classes here continue to grow which has given added impetus to our development of CAL teaching approaches.

*Gavin Reynold's Group: (left to right) Sutisa Nudmamud, Samantha Smith, (standing) Gavin Reynolds, Robert Meckin, Matt Hill*

Overall the Department is establishing a number of new strong research themes that involve interactions between a number of disciplines, and can exploit the recent advances in our subject. At the same time we are committed to research led teaching so that our students have an opportunity to experience the excitement of modern biology.

*PW Andrews*
*Chairman of the Department of Biomedical Science*
*University of Sheffield*

*Stan White's Group: (left to right) Stan White, Louise Robson, Charlotte Hill, Jon Kibble, Ian Millar, Andrew Neal, Judith Hartley*

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*PW Andrews*
*Chairman of the Department of Biomedical Science*
*University of Sheffield*

*Dear Editor,*

I read the articles in the Spring 2001 issue of the Society Magazine dealing with The Institute for Teaching & Learning. When I was appointed as a Lecturer at UCL (20 years ago), Margaret Harkness (then responsible for new staff) had only one piece of advice to give. "Avoid courses about how to teach."

Times have certainly changed. Does anyone have any views as to whether this is progress?

Yours sincerely

**David Eisner**
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*Dear Editor*

I enjoy reading the Magazine and am grateful to you for editing it. I read with interest Clive Ellory's account of the Department of Physiology in Oxford. But I was surprised that on page 2 he refers to "the work of Haldane, Bancroft and Douglas, which established Oxford as a centre for Respiratory Science".

Professor IC Ruddie and I recently wrote the memoir of Henry Bancroft, which has been published in Biographical Memoirs of Fellows of the Royal Society, London, Volume 46. We consulted the Biographical Memoir of his father, Sir Joseph Bancroft, who was a very distinguished respiratory physiologist, and worked all his life in Cambridge. I was aware that he and Haldane (in Oxford) were involved in attempts to decide whether oxygen passed by diffusion or secretion from the air in the lungs to the blood. To keep the record straight it would be helpful if Professor Ellory would provide details of Joseph Bancroft's work in Oxford.

I never worked in Cambridge, but soon after election to the Society in 1944, I attended a meeting there at which Sir Joseph gave a paper. He was asked a question. He replied that he did not know but would do an experiment and come back later with the answer. This he did. I can not recall any similar occasion!

Yours sincerely

**Professor A D M Greenfield**
*Nottingham, 13th February 2001*
*Membership Number 109245*

# MAMMALIAN TWO-PORE DOMAIN POTASSIUM CHANNELS

*The two-pore domain potassium channels are now a new and important family with characteristics of leak potassium channels, crucial to regulation of cell excitability. Here their properties are explored by Alistair Mathie and Brian Robertson.*

Over the last two or three years, a new superfamily of potassium (K) channels, the two-pore domain K channel family (2P-K), has emerged to join the established voltage-gated ($K_V$) and inward rectifier ($K_{IR}$) potassium channel families (Gray, 2000; Lesage & Lazdunski, 2000; Goldstein *et al.*, 2001). Uniquely, the individual subunits of this novel family have 2 pore regions (see Figure 1), that is to say, two separate regions of the subunit contribute to the single pore region of the functional channel. It is envisaged that two subunits come together to form functional dimers (rather than the usual K channel tetramers) although there is little direct evidence that this is indeed the case. In mammals, each subunit consists of four putative transmembrane domains (see Figure 1) as opposed to six for $K_V$ channels or two for $K_{IR}$ channels. Hence these channels are sometimes referred to, rather clumsily, as the 4TM/2PK channel family.

When members of this family of 2P-K channels are functionally expressed, they give rise to $K^+$ selective currents that, generally, are open at all voltages. Most (except, perhaps, TWIK-1 and TWIK-2) show little rectification other than that resulting from the uneven distribution of potassium ions across membranes, that occurs physiologically and which gives rise to an outward rectification often termed "open" or "Goldman-Hodgkin-Katz" rectification (see Goldstein *et al.*, 2001). An important diagnostic feature of the currents through 2P-K channels is that they are resistant to block by the classical K channel blocking drugs, tetraethylammonium ions (TEA) and 4-aminopyridine (4-AP). Thus currents through these channels have all the hallmarks of leak or background K channels that are found in most, if not all, cells and which, for many electrophysiologists, are nearly (but not quite) removed routinely from their experiments with P/N leak subtraction protocols.

At the time of writing (February 2001) there are known to be 11 mammalian genes that encode for channels in this family, but there are certainly more to come. Just how many more remains an open question. They can be divided, largely on the strength of differing functional properties, into four subfamilies. The TWIK family (TWIK-1, TWIK-2 and KCNK7), the TASK family (TASK-1, TASK-2 and TASK-3; although TASK-2 is structurally very different from TASK-1 and TASK-3), the TREK family (TREK-1, TREK-2 and TRAAK) and the THIK family (THIK-1 and THIK-2) – see Table 1. Some of these channels do not give functional currents when expressed in artificial systems but the precise number of non-functional channels is not completely clear. Certainly, KCNK7 and THIK-2 are non-functional, however, there is some debate as to whether sole expression of TWIK-1 (ironically the first mammalian 2P-K channel to be cloned) gives rise to functional channels. There is also some debate about what nomenclature should be used to describe these

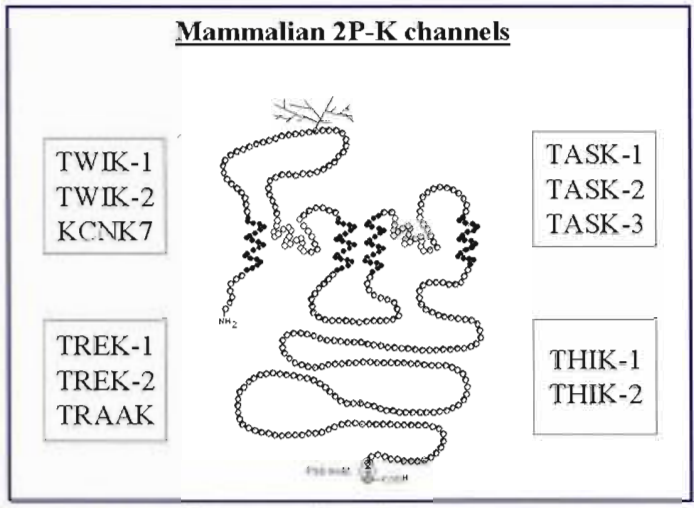


**Figure 1** ***Schematic representation of a mammalian 2-pore domain K channel.*** *A schematic representation of the 2P-K channel TASK-1 is illustrated. The two pore forming regions of the channel subunit (outline) and the four transmembrane domains (solid) can be seen. Note the short intracellular N terminus and, by contrast, the large intracellular C terminus of the channel. It is envisaged that two of these TASK-1 channel subunits come together as a dimer to form a functional channel.*

| Channel Name | Alternate Name | Specific Functional Characteristics |
|---|---|---|
| ***TWIK-family*** | | |
| TWIK-1 | KCNK1 | weak inward rectifier (or perhaps non-functional) |
| TWIK-2 | KCNK6 | weak inward rectifier (symmetrical $K^+$), inactivating current |
| KCNK7 | KCNK7 | non-functional |
| ***TASK-family*** | | |
| TASK-1 | KCNK3 | inhibited by external $H^+$ (pK = 7.3)<br>inhibited by anandamide<br>enhanced by halothane |
| TASK-2 | KCNK5 | inhibited by external $H^+$ (pK = 8.3)<br>enhanced by volatile anaesthetics |
| TASK-3 | KCNK9 | inhibited by external $H^+$ (pK = 6.7) |
| ***TREK-family*** | | |
| TREK-1 | KCNK2 | mechanosensitive, enhanced by arachidonic acid, heat, general anaesthetics & riluzole |
| TREK-2 | KCNK10 | mechanosensitive, enhanced by arachidonic acid, general anaesthetics and riluzole |
| TRAAK | KCNK4 | mechanosensitive, enhanced by arachidonic acid and riluzole |
| ***THIK-family*** | | |
| THIK-1 | KCNK13 | inhibited by halothane |
| THIK-2 | KCNK12 | non-functional |

**TABLE 1** *The mammalian 2-pore domain potassium channel family (February 2001)*

channels, with two excellent recent reviews by arguably the two leading protagonists in the field (Lesage & Lazdunski, 2000; Goldstein *et al.*, 2001) expressing different views. The choice is between the TWIK/TASK nomenclature or the KCNK1/KCNK2 nomenclature. For what it is worth, for now, we favour the TWIK/TASK nomenclature. To us, at least, it is easier to remember each channel as an individual using four letter words.

The main functional differences between the different subfamilies of these channels reflect their regulation by different chemical entities (see Table 1). So, for example, the TASK family are highly sensitive to changes in extracellular pH, the TREK family are enhanced by arachidonic acid and mechanical stretch and while the activity of some of the channels in both of these families are *enhanced* by certain volatile general anaesthetic agents (Patel *et al.*, 1999); the THIK family (at least THIK-1) are *inhibited* by the general anaesthetic agent halothane (Rajan *et al.*, 2001). Recently, some of these channels (TASK-1, TREK-2) (Czirjak *et al.*, 2000; Millar *et al.*, 2000; Talley *et al.*, 2000; Lesage *et al.*, 2000) have been shown to be regulated by G-protein coupled receptors such as muscarinic acetylcholine receptors, angiotensin II receptors, TRH receptors and metabotropic glutamate receptors. It is this plethora of regulatory pathways that make these channels so exciting. Up until now, these currents have tended to be seen as constant, stable (perhaps rather boring) background currents, acting simply to decrease cell input resistance and dampen excitability.

Now, because many regulatory pathways have been shown to act on these 2P-K channels from second to second to alter their activity, these channels can now be seen to have the potential to determine, absolutely, the excitability of a cell and how this varies both with time and with the recent experiences of that cell.

From a physiological perspective, a primary interest lies in determining which cells possess which 2P-K channels, whether they are important contributors to the background currents in these cells and if they are, determining how the excitability of that cell will be regulated. Since many of the cloned channels have only been described in the last eighteen months or so, not surprisingly, there is not a huge amount of information as to either which channels are expressed in which cells, or which of them are functionally important for a given cell. To date, best progress has been made for TASK-1. Four groups (including our own) almost simultaneously described four cell types where native background K channels displayed all the hallmarks of expressed TASK-1 channels. These are native currents in cerebellar granule cells (originally termed $IK_{SO}$), hypoglossal motoneurons, arterial chemoreceptor cells and glomerulosa cells of the adrenal cortex (Millar *et al.*, 2000; Talley *et al.*, 2000; Buckler *et al.*, 2000; Czirjak *et al.*, 2000).

Focussing on our own work, cerebellar granule cells present a particular problem with such a correlation between native and cloned channels since, at the mRNA level at least, they seem to express a number of different 2-PK channels. One of these, the TASK-3 channel, is functionally very similar to TASK-1. Recent studies have backed up the view that TASK-1 channels are crucial to granule cell excitability (Brickley *et al.*, 2001; Maingret *et al.*, 2001) but a contribution of TASK-3 channels either on their own or expressed as heterodimers with TASK-1 channels cannot be ruled out. The importance of 2P-K channels in regulating granule cell neuronal excitability is illustrated by the experiment shown in Figure 2, where a given amount of current injection can only excite the granule cell to fire action potentials when the endogenous TASK-like current ($IK_{SO}$) is blocked following activation of $M_3$ muscarinic acetylcholine receptors (see also Watkins & Mathie, 1996).

A recent paper has suggested that the background $K^+$ current in cardiomyocytes can be attributed to the 2P-K channel, TREK-1 (Aimond *et al.*, 2000) but there are no defined native correlates for any

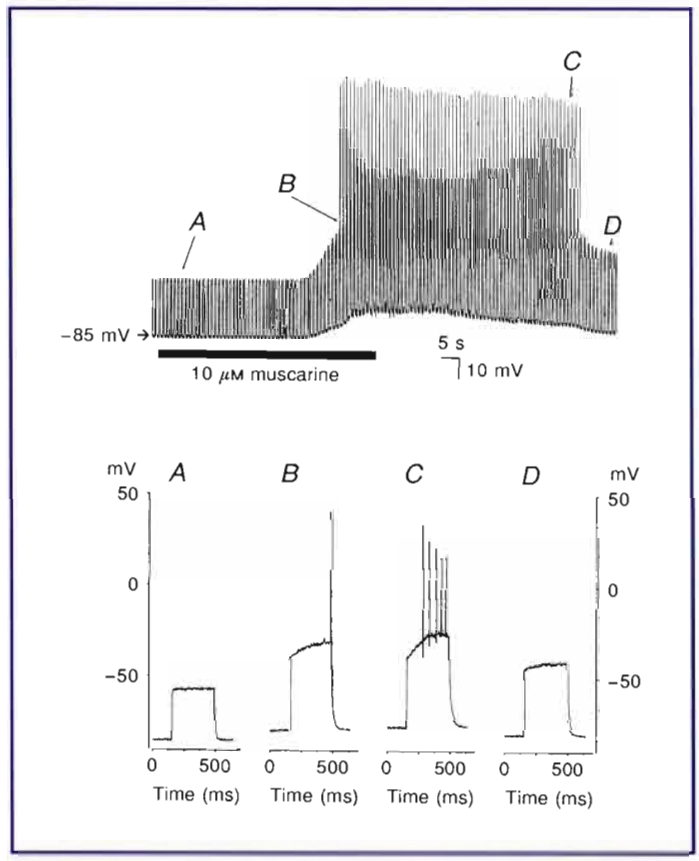


**Figure 2** ***Effect of muscarinic inhibition of the TASK-1 like, 2-pore domain K channel in cerebellar granule neurons, IKSO.*** *In current clamp recording, injection of 100 pA of current depolarised the cerebellar granule cell but did not evoke action potential firing (A). Application of 10 μM muscarine blocked IKSO and increased granule cell excitability such that the same amount of current injection now depolarised the cell sufficiently to evoke action potential firing (B, C). See Watkins & Mathie (1996) for further details.*

of the other cloned 2P-K channels so far. In some cells it may prove difficult to define the exact 2P-K channel(s) underlying a native background current. For example, in cerebellar Purkinje cells, we have observed a background $K^+$ current that shares some of the properties of cloned 2P-K channels but it is not possible to determine which 2P-K channel is predominant (Bushell *et al.*, 2000). This may reflect either a multiplicity of expressed 2P-K channels in these cells or else simply be a result of expressed 2P-K

channels not behaving the same way in artificial expression systems as they would do in their native environment.

In short, 2P-K channels represent an important new family of K channels. The activity of these channels and how this varies with time is crucial to the regulation of cell excitability. For us as physiologists, the immediate challenge is to determine which of these channels are present and functionally important in the particular cells that torment us.

*Alistair Mathie and Brian Robertson*
*Neuronal Excitability Group,*
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## Acknowledgements

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# MOLECULAR DETERMINANTS OF THE 'M-CURRENT'

*Here, Alex Selyanko explores the M-current and gives evidence that the sub-unit composition of M-channels may vary during development.*

Twenty years ago Brown and Adams discovered a new mechanism for spike adaptation in neurones – a potassium current which slowly activates on membrane depolarisation and prevents repetitive discharges (Brown & Adams, 1980). The M-current is expressed in many autonomic and central neurones where its slow activation is responsible for their 'phasic' behaviour (Figure 1A). Inhibition of the M-current by muscarinic receptor stimulants (hence the name 'M-current') or a specific blocker, XE991, causes the neurones to fire continuously (Figure 1B).

## Molecular identification

The M-current was identified after two other major voltage-dependent $K^+$ currents, the delayed rectifier and the A-current, and its channels were molecularly defined only two years ago. In 1998 Wang *et al* showed that the M-channels can be produced by heteromeric assembly of KCNQ2 and KCNQ3. These two subunits are expressed in brain and autonomic ganglia and mutations in either of them produce a benign form of epilepsy in newborn humans (Biervert *et al*, 1998; Charlier *et al*, 1998; Singh *et al*, 1998; Lerche *et al*, 1999). KCNQ2 and KCNQ3 are encoded by genes related to *KCNQ1* (Yang *et al*, 1997) and *KCNQ4* (Kubisch *et al*, 1999), mutations in which produce cardiac long QT syndrome and deafness respectively, and *KCNQ5* (Lerche *et al*, 2000; Schroeder *et al*, 2000), whose possible link to inherited diseases is still to be determined.

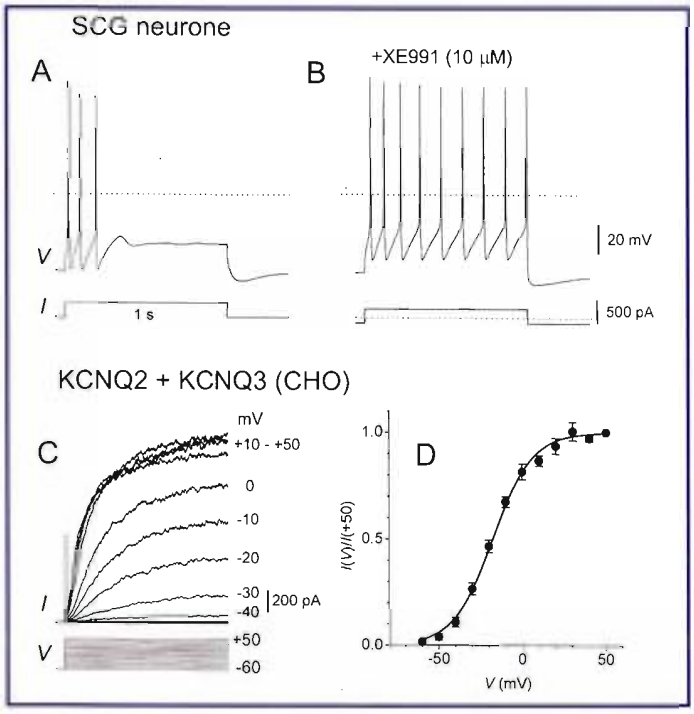


**Figure 1** *Role of the M-current in firing of a rat superior cervical ganglion (SCG) neurone (A & B) and voltage-dependent activation of M-type KCNQ2+KCNQ3 channels in transfected CHO cells (C & D). In A & B action potentials (V) were produced by 1-s depolarising current steps (I) before (A) and after (B) the M-current was inhibited by 10 mM XE991. In C KCNQ2+KCNQ3 currents (I) were activated by 10 mV-incremental voltage steps (V) from the holding potential of –60 to +50 mV. Activation curve in D was obtained by measuring deactivation tails (not shown) on stepping from –60 – +50 mV to –70 mV and fitted by the Boltzmann equation at the half-activation potential and the slope factor equal to – 18 and 12 mV, respectively. Data in C and D are from Selyanko* et al, *2000 (modified).*

KCNQ2+KCNQ3 channels expressed in mammalian cells show a slow voltage-dependent activation, with a delay of tens of milliseconds even at very positive potentials (Figure 1C). This is consistent with the time course of spike adaptation in neurones (compare with Figure 1A). The threshold of activation of KCNQ2+KCNQ3 channels is negative (close to ~-60 mV – the resting membrane potential in many types of neurone; Figure 1D), in accordance with the membrane depolarisation usually observed on muscarinic inhibition of the M-current.

Taken together, genetic evidence for the role of KCNQ2 and KCNQ3 channels in limiting neuronal excitability, their overlapping distribution in the nervous system as well as the pharmacological and biophysical similarities between the M-channels and heterologously expressed KCNQ2+KCNQ3 channels, strongly suggest that KCNQ2/3 heteromers are the major contributors to the M-current (Wang *et al*, 1998). Functional parameters of M-type KCNQ2/3 channels are also adjusted by expression of different splice variants of KCNQ2 (those with a longer C-tail make the M-current slower; Pan *et al*, 2001) and an accessory subunit of the HERG potassium channel in the heart, KCNE2 (which makes the M-current faster; Tinel *et al*, 2000).

However, there is now accumulating evidence

that within the neurone, and at some stage of its development, the subunit composition of M-channels may be different, or may even not be limited to just KCNQ2 and KCNQ3 subunits. *First*, only KCNQ2 were detected in terminal fields in the human cortex and hippocampus suggesting that homomeric KCNQ2 channels may play a specific role in regulation of action potential propagation and neurotransmitter release (Cooper *et al*, 2000). (Interestingly, an M-channel blocker linopirdine is a cognition enhancer which augments depolarization-induced transmitter release in the cortex and which is under consideration for potential treatment of Alzheimer's disease.) *Second*, during early postnatal development there is a delay in expression of KCNQ3, raising the possibility that at this stage homomeric KCNQ2 may contribute to the M-current (Tinel *et al*, 1998). *Third*, KCNQ5 is also expressed in the nervous system where it overlaps with KCNQ2 and KCNQ3 (Schroeder *et al*, 2000). Since KCNQ5 can form heteromers with KCNQ3 and when expressed heterologously, either as a homo- or heteromer, is capable of generating M-type currents, it is feasible that it may also contribute to the M-current.

## Structure and regulation

KCNQ1-5 have between 679 (KCNQ1) and 932 (KCNQ5) amino acids. Like other voltage-dependent potassium channels they have N and C termini (both intracellular), six transmembrane domains with a voltage sensor in the fourth one, and a pore-forming P-loop. A subunit assembly domain is located at the mid-point of the C terminus, and both C and N termini contain many potential regulatory sites. Although KCNQ1-5 have only 40-65% overall identity, restricted mainly to the transmembrane domains, the P-loop and the assembly domain, they all generate M-type currents with characteristic voltage-dependence and kinetics, and all can be inhibited via muscarinic M1 receptors, thus satisfying the criteria for M-channels (Selyanko *et al*, 2000). Nevertheless, KCNQ1-5 are not identical in their responses to modulation. In view of the differential distribution of KCNQ1, KCNQ4 and KCNQ2,3&5 channels, and their involvement in different functions, selective modulation of individual subunits may give ultimate control over these functions.

Just a few examples. KCNQ2/KCNQ3 currents can be increased by intracellular cyclic AMP, through a phosphorylation site in the KCNQ2 amino terminus (Schroeder *et al*, 1998). A new anticonvulsant retigabine selectively activates 'neuronal' (KCNQ2-5) M-channels by shifting their activation curves to the left, without affecting the 'cardiac' (KCNQ1) ones (Schroeder *et al*, 2001). A specific blocker of M-channels XE991 is several times more potent against KCNQ2-5 than KCNQ1 channels produced by co-expression with KCNE1 (Wang *et al*, 2000). These differences are important because even a small change in the M-current may have a strong functional effect: mutations in KCNQ2/KCNQ3 leading to a form of epilepsy reduce the M-current only by 25-30 % (Schroeder *et al*, 1998). The structural determinants of M-channel inhibition/activation by various modulators, including neurotransmitters, is a major challenge for future investigation.

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# THE IMPORTANCE OF pH HOMEOSTASIS AND ITS CORRECT NOMENCLATURE TO PHYSIOLOGY

*In this article Wilfred Widdas calls for the adoption of a terminology policy in pH homeostasis, which eliminates ambiguity and confusion*

Assuming that physiologists will continue to have a dominant role in the preclinical teaching of medical students it is important that in their teaching and in their own research they give a clear and understandable scientific description of pH concepts. The subject of pH and hydrogen ion control has grown through the twentieth century and many of the earlier simplifications are scientifically incorrect. They should now be more explicitly described, in this, the twenty first century, so that clinical and scientific aspects can be understood in simple terms without ambiguity.

Scientifically, $H^+$ is the nomenclature of the proton or nucleus of the hydrogen atom. The hydrogen atom is the foundation stone of chemistry and chemical measurements. For convenience the lightest of the elements (H) is given the mass of one Dalton (1 Da). With square brackets $[H^+]$, the same symbol has been used medically and in many papers in the biological sciences to mean the hydrogen ion concentration in watery solutions or blood plasma. This is a misnomer, since free protons only exist in a rarefied gas in a high technology machine used in nuclear physics. This misnomer is further compromised and compounded by such phrases as "The $Na^+/H^+$ Exchanger", the concept of which is of paramount importance in physiology and pH homeostasis.

The confusion in the phrase " $Na^+/H^+$ Exchanger" lies in the conveyance of a hypothetical concept that the hydrogen ions (literally protons) have come from the cell cytoplasm beyond the membrane. This is often the firm understanding of junior physiologists although there is no experimental evidence for this interpretation. It is very simple to show that each hydrogen ion ($H_3O^+$) in an average cell of ca 150 mM of monovalent ions such as KCl would be in a relevantly huge environment of positive and negative ions. In an acid solution of pH 6.2 each hydrogen ion would be surrounded by one million positively charged potassium ions and they could not migrate to the membrane protein "exchangers" through this maze of charged ionic species without contravening thermodynamic principles. The thermodynamic principle in this case is given in the second law of thermodynamics, which states that the entropy (random distribution) of an isolated system increases in a spontaneous change.

The earliest investigators of this sodium-dependent alkalinisation of cells were careful to point out that the entry of hydroxyl ions would be equivalent to the removal of hydrogen ions from the cell interior. Thus, Murer *et al.* (1) in 1976 described their findings as a "sodium / proton antiport". Terms such as NHE 2 or NHE 3 refer to a definite membrane protein, of which, the amino acid sequence has been determined and none of these terms create confusion. All that the experimental evidence clearly shows is that sodium ions enter the cell and that the external solution becomes acidic by an amount that exactly matches the sodium entry. This effect at the membrane surface would also apply if the membrane protein was able to split water into a hydroxyl and a hydrogen ion and that only neutral NaOH could penetrate the membrane and enter into the cell.

The random distribution of hydroxyl ions from the membrane proteins into the cytoplasm of a cell would produce an increase in chemical entropy and would not contravene thermodynamic principles. Further, the random distribution of hydroxyl ions throughout the cytoplasm would raise the pH value as measured by intracellular microelectrodes or fluorescent dyes. In short there is no magic in a sodium-dependent alkalinisation of cells. The ambiguity and confusion induced by the nomenclature is quite unnecessary.

There is still an ambiguity regarding the use of

$H^+$ for protons and $[H^+]$ for hydrogen ions. Both may exist in biological systems and it would be helpful if they were clearly differentiated in publications. The proton or hydrogen nucleus can be regarded as always being in a relatively much larger environment provided by a pair of electrons belonging to a larger element of the periodic table of chemical elements. Medical students would obtain an adequately understanding if taught that the two most important elements were oxygen and nitrogen when incorporated into carbon compounds of hydrophobic proteins or other carbon compounds soluble in water. A simplistic view of considerable practical value would be to include a third category of such compounds which have an intermediate set of properties, which are avid for seeking out the interface between planar water surfaces and hydrophobic proteins, including those proteins embedded in the hydrophobic lipid membranes surrounding cells. Many drugs and pharmacological agents seek the water/protein interfaces in such membrane proteins with clefts that can be filled by water.

Protons ($H^+$) certainly exist in the electron shells of the elements oxygen and nitrogen as part of many hydrophobic proteins. The protons may travel by exchange (often via hydrogen bonds) through adjacent molecular groupings. Biochemical oxidation-reduction systems involve primarily the transfers of electrons (again often eventually in pairs) and protons can also transfer with the pairs. Where oxidative metabolism is driving the flow of electrons we have purely descriptive terms for hypothetical concepts like "proton pumps" proposed to explain gastric acid secretion. However, the acid in the stomach is an accompaniment of chloride and the hydrogen ion in water, as part of hydrochloric acid, is not the proton $H^+$ but the hydronium ion $H_3O^+$ so a further stage is required for a complete understanding of this mechanism.

In water the hydrogen ion, as understood by clinicians, is regarded as being hydrated but this concept does not clarify the fact that it is a tiny positive charge in a relatively enormous electron orbit of a larger element. In the case of water it is one of the oxygen atom's lone pairs of electrons, which houses the third proton of the hydrogen ion. While the two occupied electron shells of water are roughly at right angles to one another (to give water its permanent dipole property) the third occupied electronic shell of the hydronium ion $H_3O^+$ is probably at right angles to the other two. Thus, for a simple mental picture, the hydronium may be visualized as being like an old badminton shuttle with only three feathers left. However, the mass of the oxygen (inherently electro-negative) head will tend to lead the three hydrogen nuclei, which are sharing the full positive charge. Thus, when a strong acid reacts with bicarbonate, it is just as likely for the oxygen head to combine with the delta-electropositive central carbon of bicarbonate to form ortho-carbonic acid, as it is for one of the protons to form carbonic acid. There is no firm experimental evidence for either of these interpretations but the resolution of this ambiguity should be possible in future.

In 1909, Sörensen (2) advocated that the negative of the logarithm of the hydrogen ion concentration would be a more useful measure of the relative ionic dissociation of the water molecules in enzyme studies. For buffer systems the Henderson-Hasselbalch Equation has been very useful in medicine and physiology. It should, however, be realized that pH values have no arithmetical relation to the hydrogen ion concentration but the terminology has provided a convenient expression for logarithmic concentration terms normally in the range of $10^{-4}$ to $10^{-10}$ (pH 4 to 10). In general, the logarithmic terms need careful scientific consideration; since they are not readily handled by the calculus or by simple polynomial numerical analysis. In 1981, Stewart (3) published a book on pH for biology and medicine. One of his main recommendations was that more advances in the understanding of pH problems in biological sciences would come from working directly in hydrogen ion concentrations using nanomolar quantities as units. This is recommended to be the editorial policy for physiology in the twenty first century.

The same year, 1981, saw the publication of the

Society's excellent study guide on "Acid-base balance" edited by R. Hainsworth. In that guide, R. C. Thomas used nanomolar quantities when discussing buffering and pH control. Although up-to-date at the time of publication the subject has made several important advances since then. At recent Annual Meetings of the Society the revision of the nomenclature has been adumbrated. The Press Secretary of the Editorial Board has recently outlined the challenges and dangers facing the Journal in view of the spread of "free electronic access" ideas into scientific publications. Another possible danger lies in continuing to publish expositions and papers expressed in terms of outmoded science. The present object of achieving the highest quality of science may need the adoption of a terminology policy in pH homeostasis, which eliminates ambiguity and confusion.

Holding these views, I was asked to submit an article expressing them in the Magazine for consideration by the members. However, in drawing attention to a number of aspects at present considered unsatisfactory, or of controversial ambiguity, I recognise that I hold maverick views and have no wish to press them, other than for wider consideration. Perhaps a joint committee, with a wider coverage of chemists, biochemists and other biologists should be set up. Any such committee should include clinicians that are faced directly with such acid-base problems in treating patients and in teaching the concepts of pH control to junior doctors in teaching hospitals. Much of the teaching could be simplified in so far, as is necessary for medical scientists. The introductory teaching and clear explanation of the important acid-base concepts and their control may justifiably remain one of the basic responsibilities of physiologists.

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## THE ROBERT COMLINE FELLOWSHIP IN PHYSIOLOGY

Robert Comline will be remembered with gratitude by many members of the Physiological Society. Not only did he teach physiology to generations of Cambridge students, but he was also an outstanding Society Treasurer. During his term of office the Society's assets increased five fold.

Robert's College, St Catharine's, are setting up a College Fellowship in his memory and would welcome contributions of any size from those who would like to perpetuate his memory. Cheques, made payable to St Catharine's College Development Fund, should be sent to Dr Anne Lyon, The Fellow for Development, St Catharine's College, Cambridge CB2 1RL. Dr Lyon will send contributors a Gift Aid Declaration form; by signing this, a UK tax payer can increase the value of the contribution by 28%. Dr Lyon can also provide Standing Order Mandates for those who would prefer to make their gift through regular payments.

*Tony Angel and Ann Silver*

# CAN GASES CROSS BIOLOGICAL MEMBRANES THROUGH CHANNELS?

*One of the bedrock beliefs of membrane transport physiology is that gas molecules cross membranes by diffusing freely through the lipid bilayer. Here Gordon Cooper argues that this view is in need of a reappraisal.*

It is commonly believed that gases diffuse freely through the lipid phase of cell membranes. However, in the last several years, a number of experimental observations have challenged this dogma, as summarised below. It is now becoming clear, not only that membranes can have an extremely low gas permeability, but that in some cases "gas channels" appear to augment membrane gas permeability.

## Membranes with low gas permeability

Although hints were available earlier, the conclusive evidence that membranes might have extremely low permeabilities to gases came from Walter Boron's laboratory at Yale in 1994 (Waisbren *et al.*, 1994). The chief and parietal cells of the gastric gland are presented with a very hostile environment, namely a pH as low as 0.7 and the presence of the protease pepsin. The apical membrane of these gland cells provides the barrier layer, which prevents the cells from digesting themselves. Boron's group studied single micro-dissected gastric glands using the microperfusion techniques first described for renal tubules (Burg *et al*, 1966). When the peritubular (blood-facing) side of the glands were exposed to a solution containing 1% $CO_2$/5mM $HCO_3^-$ there was the expected decrease in intracellular pH $(pH_i)^\dagger$ as $CO_2$ entered the cell and formed $H^+$ and $HCO_3^-$, indicating that the basolateral membrane of the cells is $CO_2$ - permeable. However, when the gland lumen was exposed to a solution containing as much as 100% $CO_2$/22 mM $HCO_3^-$ there was no change in $pH_i$. Moreover, exposing the bath to 20 mM $NH_3/NH_4^+$ at pH 7.4 caused a significant $pH_i$ increase, as $NH_3$ enters the cell across the basolateral membrane and combines with $H^+$ to give $NH_4^+$, whereas exposing the lumen to a 25 times greater concentration of $NH_3$ elicited no change in $pH_i$. Thus, the apical membranes of chief and parietal cells have no demonstrable permeability to $CO_2$ or $HCO_3^-$, nor to $NH_3$ or $NH_4^+$ (Waisbren *et al*, 1994).

## Contribution of Channels to Membrane Gas Permeability

It is clear that specialised cells can construct membranes impermeable to gases. A question that then arises is whether cells can use channels to increase gas permeability. Three recent studies indicate that the movement of gases through channels can contribute to membrane gas permeability.

### The water channel aquaporin-1 is permeable to $CO_2$

Cooper and Boron (1998) examined the effect of expressing the aquaporin-1 water channel protein AQP1 on the $CO_2$ permeability of oocytes. Figure 1 shows experimental traces from three oocytes expressing different amounts of AQP1. The rate of $CO_2$ -induced acidification is an index of $CO_2$ permeability – the greater the acidification rate, the higher the $CO_2$ permeability. The level of AQP1 expression was judged from the time taken

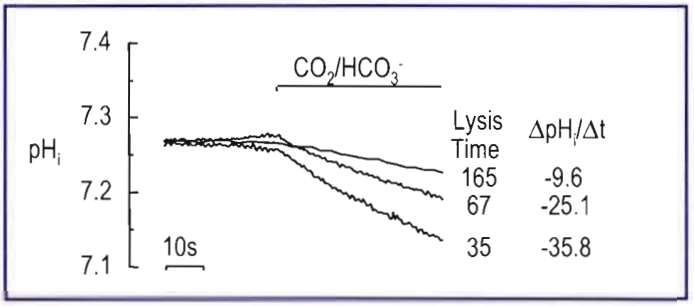


**Figure 1** *Effect of expressing AQP1 on oocyte $CO_2$ permeability. (A) Three oocytes with increasing levels of AQP1 expression were exposed to $CO_2$ and the rate of acidification measured. Reproduced from Cooper & Boron (1998) by permission of the American Physiological Society.*

for the oocytes to lyse when exposed to de-ionised water. Under these conditions the oocyte gains water osmotically, swelling and eventually lysing. Expression of AQP1 introduces a pathway for this osmotic water movement, so the oocytes lyse faster the more AQP1 they express. Figure 1 shows that an increase in AQP1 expression is

paralleled by an increase in $CO_2$ permeability. These results are consistent with AQP1 being permeable to $CO_2$. However, they cannot exclude other possibilities, particularly that: (i) the oocyte contains a native gas channel that is induced by AQP1; and/or (ii) that over-expression of AQP1 alters the membrane lipid composition, making the membrane leakier and thus more permeable to $CO_2$.

To distinguish these three options, we examined the effect of the mercurial agent pCMBS on the AQP1-dependent increase in $CO_2$ permeability. Mercurial compounds such as $HgCl_2$ or pCMBS prevent the movement of $H_2O$ through AQP1 (Preston *et al*, 1992) by interacting with a critical cysteine residue (C189). When C189 is mutated to a serine (the C189S mutant), the movement of $H_2O$ through the resulting channel is no longer prevented by mercurials (Preston *et al*, 1993). In a similar way, pCMBS inhibited the AQP1-dependent increase in $CO_2$ permeability (Figure 2A). As pCMBS does not interact with membrane lipids, the third option – that AQP1 increases $CO_2$ permeability by altering lipid composition – can be discounted. In order to address the second possibility, that AQP1 induces a native gas channel, we used the C189S mutant of AQP1. Expressing C189S increased oocyte $CO_2$ permeability to the same degree as expressing wild type AQP1. However, the C189S-dependent increase in $CO_2$ permeability was no longer inhibited by pCMBS (summarised in Figure 2B). Thus, as well as being permeable to $H_2O$, the AQP1 channel can act as a conduit for the entry of $CO_2$.

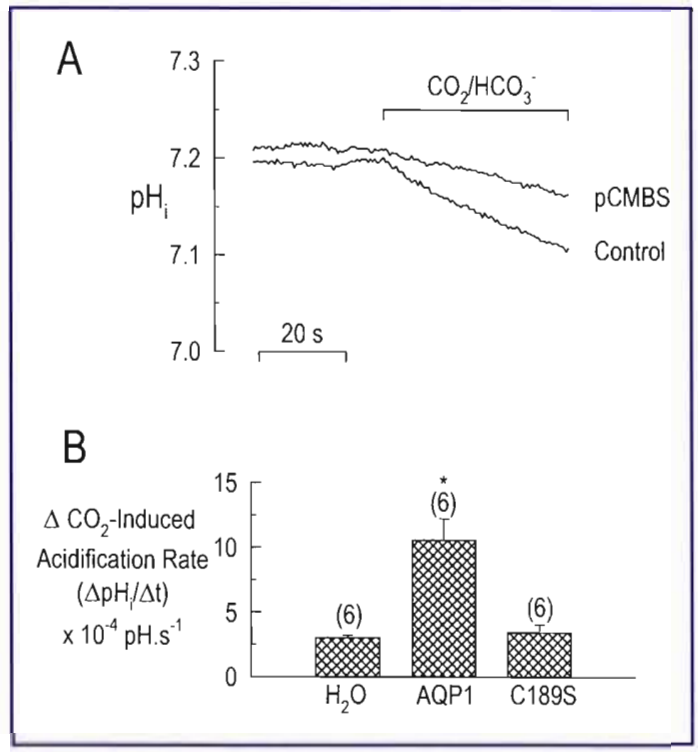


**Figure 2** *Effect of pCMBS on the $CO_2$ permeability of AQP1. (A) A single oocyte was exposed to 1.5%$CO_2$/10mM $HCO_3$ before and after a 15 minute incubation in 1mM pCMBS. (B) Summary of changes in CO2-induced acidification rate produced by pCMBS. Each bar indicates the mean of paired differences before and after exposure to pCMBS. * indicates that the change in rate was significantly larger compared to the other 2 groups. Reproduced from Cooper & Boron (1998) by permission of the American Physiological Society.*

**The $CO_2$ permeability of red blood cells is inhibited by DIDS**

The red blood cell membrane has an extremely high permeability to $CO_2$, a property that goes hand in hand with the major role of the red cells (i.e., the transport of respiratory gases in the blood). The stilbene derivative DIDS, a compound commonly used as an inhibitor of $HCO_3^-$ transporters, inhibits the $CO_2$ permeability of red blood cells by about 90% (Forster *et al*, 1998). However the inhibitory action of DIDS on red blood cell $CO_2$ permeability does not involve an interaction with Band 3 (i.e., the red-cell $Cl^-$-$HCO_3^-$ exchanger) or with intracellular carbonic anhydrase. Moreover, DIDS does not interfere with membrane lipid composition. Forster *et al.* thus concluded that the transport of $CO_2$ into the red blood cell involves a protein-mediated pathway. The water channel AQP1 is abundant in the red blood cell, and it is intriguing to speculate that this protein may account for part of the protein-mediated transport of $CO_2$ in these cells.

**The $NH_3$ permeability of the peribacterial membrane is protein-mediated**

In legumes, biological nitrogen fixation (i.e., $N_2 + 3H_2 \rightarrow 2\ NH_3$) occurs in specialised root nodules that play host to the bacterium *rhizobia*. The *rhizobia* are enclosed in a compartment bounded by the peribacteroid membrane. The symbiotic arrangement found in the root nodules of these plants is of particular interest with respect to gas transport. High levels of $O_2$ inhibit the nitrogenase enzyme in *rhizobia*, which is responsible for nitrogen fixation. For efficient

nitrogen fixation, the peribacteroid membrane needs to limit $O_2$ influx whilst maintaining a high permeability to $N_2$ and $NH_3$. Recently it was demonstrated that about half of the movement of $NH_3$ across the peribacteroid membrane is temperature-dependent and can be inhibited by pCMBS (Niemietz & Tyerman, 2000). Both of these properties are characteristics of a protein-mediated process. The authors suggested that a plant water channel called nodulin-26, found at high levels in the peribacteroid membrane, might account for the protein-mediated component of $NH_3$ transport.

## Conclusion

The studies discussed above illustrate how our commonly held ideas about the movement of gases across membranes need to be re-evaluated. On the one hand, as a matter of survival, cells can make membranes impermeable to gases. On the other hand, movement of gases across membranes can be protein-mediated. It is interesting to speculate that this protein-mediated gas transport may play an important role in biological functions, such as nitrogen fixation or renal bicarbonate reabsorption.

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† The changes in $pH_i$ associated with the movement of NH3 and $CO_2$ are reviewed by Boron (1992).

# HYPOGLYCAEMIA AND CENTRAL WHITE MATTER: MECHANISMS OF INJURY AND NEUROPROTECTIVE STRATEGIES

*The brain is vulnerable to low blood glucose, and hypoglycaemia is a major problem for diabetics. Here Angus Brown explains how this hypoglycaemia may cause cellular damage to the white matter.*

Although the brain comprises only 2% of body weight, it accounts for 75% of the body's daily requirement for glucose. This high metabolic demand requires an uninterrupted blood supply, which renders the brain vulnerable to shortfalls in delivery of blood-borne glucose. This critical dependence of the human central nervous system (CNS) on glucose has led to the evolution of complex homeostatic mechanisms that maintain blood glucose concentrations within strictly regulated euglycaemic (normal) levels, mainly by the actions of insulin and glucagon. However, this homeostatic system can be disrupted by disease, leading to life-long problems of "managing" blood glucose levels.

## Type-1 diabetes, hyper- and hypoglycaemia

People suffering from Type-1 (insulin-dependent) diabetes are unable to manufacture insulin due to autoimmune destruction of pancreatic Beta-cells. Since insulin maintains blood glucose in the euglycaemic range by facilitating transport of glucose from blood into cells, patients with Type-1 diabetes cannot maintain blood glucose at euglycaemic levels, and periods of both hyperglycaemia (higher than normal blood glucose) and hypoglycaemia (lower than normal blood glucose) are inevitable. Hyperglycaemia in particular is implicated in the long-term morbidity (neuropathy, retinopathy and nephropathy) that typically afflicts Type-1 diabetics, and the main goal of diabetic therapy is thus to prevent hyperglycaemia by introduction – typically by injection – of exogenous insulin. However, it is a cruel fact that diabetics who actively strive to maintain euglycaemia often fall victim to hypoglycaemia, due to the difficulties of matching insulin delivery to minute-by-minute blood glucose concentration. Indeed, fear of hypoglycaemic episodes is the major deterrent that prevents diabetics from maintaining a rigid regime of insulin therapy and achieving euglycaemia.

While the avoidance, and complications, of hyperglycaemia have received the majority of attention, it is increasingly appreciated that hypoglycaemia is a major factor in decreased quality of life for most diabetics and their families. This reflects the need for continual hypoglycemia avoidance strategies, as well as the potentially serious consequences of suffering a severe hypoglycaemic episode. When blood glucose falls to hypoglycaemic levels (defined by the British Diabetic Association as below 4 mmol/l) there is a series of responses, associated with both autonomic and neurological symptoms, whose intensity increases with the degree of hypoglycaemia (Figure 1). The detection and correct interpretation of responses to mild hypoglycaemia can act to warn the patient of an impending hypoglycaemic episode, and therefore to take suitable counter-measures. However, hypoglycaemia is not always detectable, for a variety of reasons (e.g. hypoglycaemia unawareness, nocturnal onset), and all Type-1 diabetics will inevitably endure hypoglycaemic

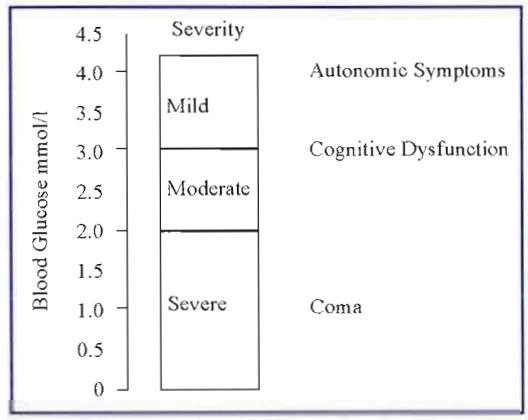


**Figure 1** *Correlation between blood glucose levels and symptoms of hypoglycaemia. The blood glucose levels reflect those in a normal non-diabetic person, as the levels in a diabetic are prone to fluctuation.*

episodes. It is estimated that the typical Type-1 diabetic will endure 70 episodes severe enough to require assistance, and 3500 mild episodes, of hypoglycaemia in his/her lifetime [1]. There is increasing evidence that the cumulative effects of these repeated hypoglycaemic episodes eventually result in permanent CNS injury, reflected in, among other deficits, impaired memory and decreased cognitive ability.

## Mechanism of white matter injury

It is commonly accepted that the brain contains no endogenous energy supplies, and relies solely on the blood for nutrients. However, a recent study from our laboratory, using the adult rat optic nerve (RON) as a model of central white matter, demonstrated that central white matter does contain a utilizable energy source in the form of glycogen within astrocytes [2]. The

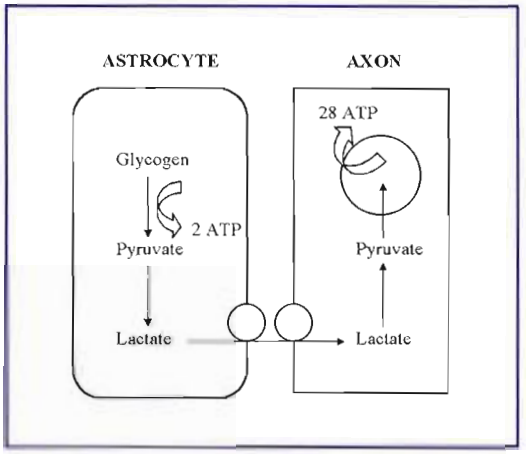


**Figure 2** *Schematic illustrating how glycogen stored in astrocytes appears to fuel axons in the adult RON in the absence of glucose. Astrocyte glycogen is broken down to lactate, which is transported to the extracellular space via a monocarboxylate transporter (most likely MCT1). It is then taken up by a monocarboxylate transporter (most likely MCT2) into axons and is metabolized oxidatively.*

astrocytic glycogen is metabolized to lactate, which is then transported into axons where it sustains function for over 30 minutes after withdrawal of glucose (Figure 2). Beyond this point glycogen stores are exhausted, and axon function fails. We were able to pharmacologically up- and down-regulate glycogen levels resulting in, respectively, increased and decreased latency to axon failure during hypoglycaemia. These results are encouraging, since they suggest that at least certain parts of the CNS are not solely at the mercy of blood to deliver nutrients, but can use an endogenous energy supply to maintain function during hypoglycaemic episodes. This important role for glycogen in preventing hypoglycemia-induced CNS injury is being pursued in our laboratory.

Once astrocytic glycogen energy reserves are exhausted during a hypoglycaemic episode, CNS injury is inevitable. Almost all of the previous studies on the effects of hypoglycaemia on the CNS have concentrated on gray matter areas, where glutamate excititoxicity appears to be the major cause of neuronal death [3]. In contrast, almost nothing is known about how hypoglycaemia affects white matter areas, even though they comprise 50% of brain volume and are fundamental to brain integrity. We found that a 1-hour period of hypoglycaemia (i.e. no glucose in the artificial CSF bathing the RON), followed by a 1 hour recovery period in control artificial CSF containing 10 mM glucose, resulted in approximately 50% reduction in RON function, indicating that irreversible injury had occurred. Neuronal function was assessed by recording the stimulus-evoked compound action potential (CAP) from the RON. Repeating the experiment in a $Ca^{2+}$-free artificial CSF resulted in no functional loss, implying that hypoglycaemia-induced injury is a $Ca^{2+}$-dependent process [4]. The lack of glutamatergic synapses in white matter implies a different mechanism of cell death from the glutamate excitotoxicity in gray matter. In order to evaluate $Ca^{2+}$ movements during hypoglycaemia, we recorded extracellular free $Ca^{2+}$ using $Ca^{2+}$-sensitive microelectrodes. Extracellular [$Ca^{2+}$] fell with a similar time course to the progressive failure of the CAP, suggesting that $Ca^{2+}$ moves into intracellular compartments as cellular injury occurs. Immunocytochemical studies demonstrated that the RON contains exclusively L-type $Ca^{2+}$ channels, which are located on both axons and astrocytes [5]. Application of L-type $Ca^{2+}$ channel blockers during the hypoglycaemic insult caused decreased $Ca^{2+}$ influx and was neuroprotective, implicating L-type $Ca^{2+}$ channels as a route of toxic $Ca^{2+}$ influx. Inhibitors of $Na^{+}$-$Ca^{2+}$ exchange similarly decreased $Ca^{2+}$ influx and were neuroprotective.

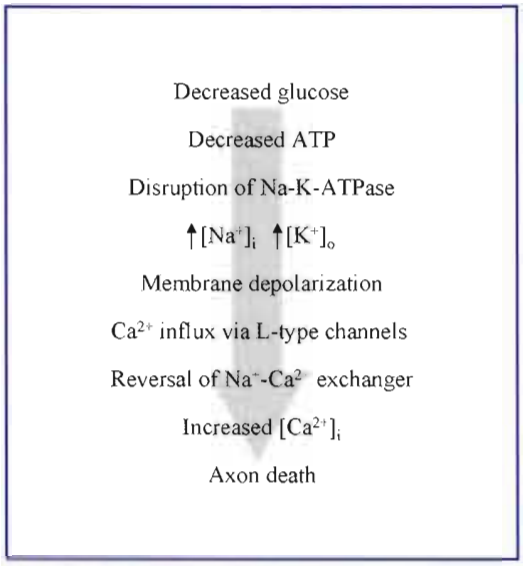


**Figure 3** *Illustration of the sequence of hypoglycaemia-induced axon death in the adult RON. Decreased glucose levels lead to decreased levels of ATP, which are required to maintain transmembrane ionic gradients via the action of the Na-K-ATPase. The resulting increase in extracellular $K^+$ and intracellular $Na^+$ leads to membrane depolarization and activation of voltage gated $Na^+$ and $Ca^{2+}$ channels. The Na+ and $Ca^{2+}$ influx, coupled with membrane depolarization leads to reversal of the $Na^+$-$Ca^{2+}$ exchanger, causing more $Ca^{2+}$ to be pumped into axons. The $Ca^{2+}$ influx results in axon death, probably by the actions of $Ca^{2+}$-activated enzymes.*

It thus appears that toxic $Ca^{2+}$ influx, presumably directly into axons via L-type $Ca^{2+}$ channels and reverse operation of the $Na^+$-$Ca^{2+}$ exchanger (Figure 3) mediates hypoglycaemic axon death in this preparation [4].

## Future directions

The ultimate goal for research into Type-1 diabetes is the correction of insulin deficiency. Eventually this is likely to be achieved by introduction of viable insulin-secreting cells into patients, whether by implanting clusters of insulin-secreting cells, by stem cell technology or by gene therapy. However, the successful clinical introduction of these technologies is at least several years in the future. Until a cure for Type-1 diabetes is a reality, research must continue into areas that will improve the quality of life for diabetic patients. These include improving glucose sensing technology, and developing short- acting insulin, inhaled insulin and insulin analogues to help maintain euglycaemia. In addition, investigating the mechanism(s) by which hypoglycaemia injures the CNS at the cellular level is a priority. This will hopefully allow development of neuroprotective strategies that will spare CNS function during the inevitable periods of hypoglycaemia endured by all Type-1 diabetics.

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## TALKING TO THE PRESS

One of our members, Professor Mary Forsling, was prepared to put her head over the parapet and talk to the press about her work, which partly concerned the drug MDMA. The present government assure us that in their next term of office they will be concerned to address the current hostility between the public and scientists – but this is going to involve scientists trying to understand the public's point of view as well as the other way round. Increased communication is vital – please do respond to my pleas to speak to the press, silence is so frequently misconstrued. Currently, the majority of television and radio interviews are taken by a handful of our members. I think it is time for the rest of you to stop hiding your lamps under bushels. *Maggie Leggett*

## MAKING AN IM*PRESS*ION

Andy Warhol promised me 15 minutes of fame, and I finally received it! At an early age, my younger daughter declared a desire to be rich and famous. To avoid possible disappointment, I suggested that there were different sorts of fame, pointing out that scientists and doctors achieve some degree of fame through the groups they teach. She was, however, adamant that fame could only be achieved through the media. So just how does that happen?

It is always gratifying when one's abstract is accepted for a scientific meeting, and so I was pleased when my work was selected as an oral communication for last November's meeting of the Endocrinology Society. My research centres on modulation of pituitary hormone release by melatonin and gonadal steroids, and I have shown that melatonin and its precursor serotonin influence vasopressin release. My abstract at the meeting concerned 3,4methylenedioxymethamphetamine (MDMA or "ecstacy"), which is believed to act via serotonin. By chance, I learnt that MDMA could produce water retention, and that this might have led to some of the high profile deaths that have been reported. This hyponatraemia could have resulted from inappropriate vasopressin secretion. Consequently, I collaborated with colleagues from King's College and Imperial College on a pharmacokinetic study centred on MDMA.

We did, indeed, find that MDMA stimulated vasopressin release. Surprisingly, however, during the first couple of hours of the study, plasma vasopressin inversely correlated with MDMA. This might have resulted from the formation of an active metabolite, and the reduced MDMA being associated with greater formation of the metabolite and enhanced vasopressin release. MDMA can be metabolised by two pathways and, with the Drug Control Centre at King's College and the Department of Pharmacy, I looked at the effect of the major metabolite 4-hydroxy-3-methoxymethamphetamine (HMMA) on the neurohypophysial hormone release from rat hypothalamic explants in vitro. We found that both MDMA and HMMA stimulated vasopressin release, HMMA being the more potent. It was this work that formed the basis of my abstract.

Pleasure at the acceptance of my abstract was followed by great surprise when the Endocrinology Society asked me if the results could be included in the meeting's press release – I would be asked to approve the wording. I agreed. I have long been concerned that children acquire much information that they never revisit, and are kept largely ignorant of the way their body functions.

Apprehension only began to kick in when the Society rang with the dates of the press release

and to confirm that I would be available to talk to journalists. Oh why hadn't I taken that course on working with the media? But then, as later, the staff from the Society were very reassuring. All calls would go to the Society, and I would never have to give an interview immediately if I felt unprepared. I should also avoid giving personal views on the use of "ecstacy". Their main advice was to give two or three main points and a take home message.

I put the phone down and worked on the problem. Summarising my work would be relatively easy. The message should be that, while it is important to maintain hydration after taking "ecstacy", one should not over do it. This was particularly important for young women, as women of reproductive age are much more likely to suffer serious side effects on developing low plasma sodium.

Nothing was to appear in the press before my presentation at the meeting, but the preceding week was a flurry of activity, with calls from *Newscientist* and *The Times*, *Independent* and *Telegraph*, as well as the Medical Channel (Sky TV's channel for doctors). All the journalists were well informed and helpful. On hearing it was my first interview, Andy Coghlan from NewScientist offered to send me a copy of the piece for comment. My confidence grew, and the pieces that appeared gave a fair summary of the topic. other workers in the field had obviously been consulted so that the reports were well balanced and, furthermore, I was not misquoted.

Rachel Lawson from Radio 1 interviewed me at the meeting. She immediately put me at ease. We had to go over and adjust the questions beforehand, and I checked how I should pitch my responses. Any sections that I was not happy with were redone. Rachel finally left to interview some "ecstacy" users. I was impressed with the way the information was presented in the resultant broadcast. Interviews for Radio 5, German TV, Austrian radio and London Metro followed.

The excitement abated, though emails still trickle in from across the globe. Was this all worthwhile, or just "hype"? While I was apprehensive at first, I found the experience generally enjoyable. It is hard to say how much impact the message made, but I hope I contributed to the demystification of things medical and scientific. My elder daughter, who only heard the headlines on Radio 1 and so was unaware of my contribution, had discussed the topic with her friends at University. Queries have come from those working on the problem of drugs, both in charities and the police. Hyponatraemia following MDMA ingestion may not be a major problem, but if one person is helped, it will have been worthwhile.

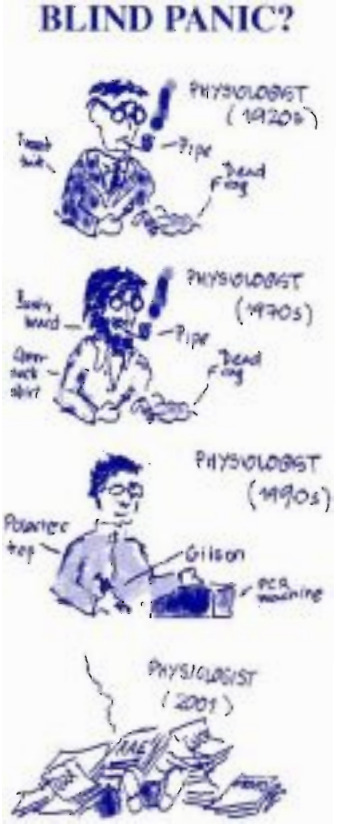
*Mary Forsling*
*Neuroendocrine Laboratories,*
*Guy's, King's and St Thomas's School of Medicine*

*The Physiological Society would like to thank The Endocrinologist for their kind permission to reproduce the above article, which appeared in their Spring 2001 newsletter, issue number 59.*

**BRITISH NEUROENDOCRINOLOGY GROUP**

Our members may also wish to note that the British Neuroendocrinology Group have been re-named, and are now called the British Society for Neuroendocrinology.

# BLIND/UNBLIND/DOUBLE-BLIND... BLIND PANIC?




Careers in academic scientific research contain many hidden surprises. One of these is the sometimes bizarre bureaucracy, and (sadly) increasing managerialism, of the contemporary British University. Like many things associated with getting older, this creeps up on you stealthily. As a Ph.D. student, postdoc, or newly-appointed lecturer, you live in blissful ignorance of quality audits, subcommittees, working parties, and minutes. Not to mention concepts like "standardization", "best practise" and "transparency". But if you serve enough time in a UK University, the day will come when you suddenly realise, to your horror, that you actually recognise these terms. I stress "recognise" – you won't, of course, actually know what they mean. But you will definitely have heard someone use them somewhere – probably at a subcommittee meeting.

And that's when you come to a terrible realisation: you have become ... an academic.

Once you reach this stage, there is no denying the truth – you have joined a sinister cult, with rituals and a vocabulary all of its own. For instance, the day before writing this column, I sat through nearly three bottom-numbing hours of an Examinations Officers Subcommittee Meeting. The main item of (extremely lengthy) debate was whether our existing procedures for marking students' exam essays were better described by what our compendious "University Examinations Procedures and Regulations Handbook" called "Universal blind double-marking" or the subtly different "Universal *un*-blind double-marking". Quite what the difference was between the two would have taxed a team of highly paid lawyers, let alone a group of bemused scientists. After nearly two hours of circuitous discussion, I had the distinct feeling that the *most* appropriate description would be "Blind leading the blind double-marking". Or perhaps the more hopeful "Blind faith double marking". We did not, of course, include these thoughts in the official subcommittee minutes. Once the exams start, and the piles of papers arrive on my desk, the reality may well be closer to "Double blind-drunk double marking"...

What I am getting at here is that life in UK academic science these days can stray a long way from curiosity-driven research – or even from teaching, which at least involves communicating research-derived knowledge and ideas. Instead the daily routine can often resemble the kind of large-company administrative Kafka-fest celebrated (if that's the right word) in Scott Adams' *Dilbert* cartoons. For "cubicle" read office, for "restructuring" read departmental reorganization, for "quality assurance" read TQA, and for "management consultants" read "pre-RAE internal audit team"... Or even just "management consultants", if your University is really forward-looking. It certainly doesn't seem that far away from my present reality. So be warned. And remember to close those loops and have your audit trail in place...

*"Dr Mark Cain"*

...is considering writing a dictionary of managerial terminology directed at the working scientist. When not busy with this or his quality audit trail he can be found "thinking outside the box", or planning his early retirement.

# JOINT MEETING WITH THE GERMAN PHYSIOLOGICAL SOCIETY

*15 – 19 March 2002, Tübingen, Germany*

The Physiological Society and the German Physiological Society are organising a joint meeting from Friday 15 March to Tuesday 19 March 2002. For up-to-the-minute details of the programme and designated speakers see the meeting website on www.uni-tuebingen.de/DPG2002. Tübingen is an attractive town about 30 km from Stuttgart Airport and well situated for road communications north and south. However, accommodation is limited and members will need to organise their registration early in 2002 to be sure of being able to stay in the town. Both Societies expect considerable numbers of members to attend.

The Society is putting aside funds to assist Affiliates and Members with the additional costs of travel/accommodation. Applications for grants are invited: there is a form on pages 37/38 of this issue of the Magazine. The closing date for applications is Friday 28 September 2001. Applicants will be notified the result by the end of October, in time to submit their abstract by the closing date for abstract submission at the end of November.

# INTERNATIONAL WORKSHOPS

Last year, the International Office instituted a scheme for sponsoring International Workshops for Young Physiologists. These are aimed primarily at young physiologists from East Europe and the ex-CIS states (though young physiologists from the U.K. and elsewhere are very welcome to join in).

The first of these, on the theme of "Membranes and Signalling", was held last September in Kiev (Ukraine), hosted by Professor Platon Kostyuk and Dr. Elena Lukyanetz of the Bogomoletz Institute of Physiology. It was attended by 60 young visiting scientists – 18 from the Russian Federation ( including one from Krasnoyarsk in Siberia!), 3 from Bulgaria, 1 from Georgia, 5 from Slovakia and 17 from other parts of the Ukraine – plus 12 from other Institutes in Kiev. Physiological Society members Stuart Bevan, Tom Bolton, David Brown, David Eisner, Alison Gurney, Ole Petersen, Emil Toescu, Alexei Tepikin and Alex Verkhratsky went over to talk to the young scientists. Other speakers were Olga Garaschuk from Munich and P.G. Kostyuk, O.A. Krishtal, E.A. Lukyanetz, M.F. Shuba, Ya.M. Shuba, V.I. Skok and N.S. Veselovsky from the Bogomoletz Institute itself. In the afternoons, members of the Bogomoletz held a series of laboratory demonstrations and practical sessions, and at lunchtimes and in the early evenings the young visiting scientists mounted posters showing some of their own work, which they discussed with the visiting speakers. On the final day, prizes were presented for the best three posters for each of the preceding sessions. (You can still find a copy of the full programme on the Bogomoletz Institute's web-site at http://www.biph.kiev.ua) Of course, the social side was not forgotten, as the picture below indicates.

Platon Kostyuk and Elena Lukyanetz did a superb job as local organizers, and the demonstrators worked really hard (even curtailing their traditional summer vacation to set it up). I think we were all struck by the enthusiasm of the participants – especially remembering that they had to find their own fares to get to Kiev (in many cases out of their own meagre salaries). Indeed, for some of them, it was the first opportunity they had had to present and discuss their work outside their own labs. From the UK's viewpoint, perhaps the greatest bonus lies in the contacts made with bright (and well-trained) young physiologists from that part of the world, which has already led to the development of two collaborative research ventures with U.K. labs, with more in the pipeline.

This year we plan to repeat the exercise, this time in Prague in the Czech Republic (see box announcement). The theme will be

*Farewell party at the Kiev workshop. (Can you spot your International Secretary?)*

"Experimental Methods for Brain Studies in Health and Disease". It will be hosted by Professsor Eva Sykova, of the Institute of Experimental Medicine, and will take place between October 23rd and 27th. The first two days will again be given over to seminars and practical demonstrations. This will then be followed by the Fourth Conference of the Czech Neuroscience Society. The U.K. emissaries to the Workshop have been invited to give talks at this Conference and the Workshop speakers will be able to present their posters for discussion.

## Junior Fellowships

Members of the Society are reminded that last year the International Office also started a Junior Fellowships scheme for young physiologists (at postgraduate or junior postdoctoral level) in East Europe, the ex-CIS states or the Third World. The aim of this scheme is to encourage young physiologists in these countries to stay in science in their own country and establish their future research careers in Physiology (or related sciences). The Fellowships are for up to two years duration, and will include a personal salary supplement of up to £1000 p.a., and some modest support for their research costs. There are two key elements to the scheme. First, each Fellow must be sponsored by a U.K. member of the Physiological Society. Second, the Fellow will be required to spend a period of at least 3 months in the sponsor's laboratory (or another U.K./Eire laboratory) during the course of his or her Fellowship. The costs of travel between the Fellow's home institution and the U.K. laboratory will be covered but it is assumed that the U.K. lab will have (or be able to obtain) funding to support the Fellow's accommodation, subsistence and research costs in the U.K.

So, if you know of any promising young scientist worthy of support who you would be prepared to sponsor, please let me know. You will need to provide (a) the prospective Fellow's C.V., (b) a one-page outline of the proposed research (including that in the U.K.), (c) a statement from the Fellow's home institution that they will accommodate the Fellow during the tenure of the Fellowship, and (d) a statement from you (the sponsor) that you can cover the costs of the Fellow's stay in the U.K. (Please contact me if the latter proves an insuperable problem.)

## Recycling of redundant equipment

Many laboratories overseas are less well-equipped than those in the U.K. and have financial or other difficulties in acquiring equipment for teaching and research. On the other hand, some U.K. laboratories or departments may well have redundant but quite serviceable equipment 'surplus to requirements' which they don't know what to do with. FEBS (the Federation of European Biochemical Societies) has a well-developed scheme for 'recycling' such redundant equipment to less well-off laboratories (see http://www.febs.unibe.ch/Activities/SARS.htm). They collect together redundant apparatus, refurbish it as necessary, then circulate constituent societies with lists at regular intervals, and ship the apparatus free of charge to those departments and laboratories that require them.

The question arises: should the Physiological Society consider setting up some similar scheme? It obviously costs a fair amount of money for storage and shipment, and needs quite a lot of organization. However, I think there would be a demand for it by impoverished labs overseas. I would certainly appreciate views on this, especially from anyone willing to help organize a scheme or who has good ideas about how it might best be run. In the meantime, perhaps any department or lab with surplus equipment in working order, or anyone who has had requests for equipment from overseas, could let me know. The International Office might then be able to put the two together and perhaps provide some short-term financial assistance toward the shipment costs.

*David Brown,*
*International Secretary.*

# ADVANCED WORKSHOP IN NEUROSCIENCE FOR YOUNG PHYSIOLOGISTS

*"Experimental Methods for Brain Studies in Health and Disease"*

**Institute of Experimental Medicine, Czech Academy of Sciences, October 23– 27 2001**

*Sponsored by the Physiological Society*

The workshop will consist of a series of lectures, seminars and practical demonstration sessions. It is aimed primarily at young physiologists from East Europe and the ex-CIS states, but is also open to young physiologists from the U.K. and elsewhere in Europe. The seminars and practical sessions will take place on 23rd-25th October, and will be followed on 26th and 27th by the 4th meeting of the Czech Neuroscience Society. This will include special lectures devoted to the topics of the workshop and a special poster session for workshop participants.

Speakers will include J. Abbott, J.Ashmore, T.V.P. Bliss, F.A. Edwards, E.F. Evans, M. Hausser, D.C. Ogden, J. O'Keefe, O.H. Petersen, R.C. Thomas and A. Verkhratsky (from the UK), C. Nicholson (USA), and J. Bures, A. Chvatal, A.A. Fenton, M. Hajek, P. Mares, J. Syka, E. Sykova and L. Vyklicky (Czech Republic).

Practical demonstration sessions will be provided on the following topics: approaches to recording from neurones in c.n.s. slices and cultured cells; electrophysiological and morphological properties of glial cells; diffusion in the brain measured with ion-sensitive microelectrodes (ISM); $K^+$, pH and $Ca^{2+}$ measurements using ISM; auditory neurophysiology; experimental epilepsy and evoked potential recording; behavioural and electrophysiological methods for studying spatial memory.

Practical demonstrations will be limited to 50 participants. All costs of attending the workshop and subsequent meeting for participants from East Europe and the ex-CIS states (except fares) will be covered by a grant from the Physiological Society. (Limited help with fares from these countries may be possible in special cases: those requiring such help should contact Professor D A Brown, address below. U.K. physiologists who wish to attend should also contact Professor Brown.)

**Applications should be made by July 31 2001 to Professor E Sykova.**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# YOUNG PHYSIOLOGISTS SYMPOSIUM
## University of Dundee, 16th – 17th January 2001
*"Membrane Function in Health and Disease"*

A freezing cold Tuesday morning in January saw a huddle of young physiologists descend on the Ninewells Institute of Child Health in Dundee. The audience was varied with delegates having come from as far as Belgium, as well as there being a good local contingent. This was my first attendance at such an event and I was interested to find a range of attendees from first year PhD students through to post-doctoral scientists.

Dr Catherine Goddard (from Cambridge University), the keynote lecturer, started us off with an insight into the use of mouse models for the understanding and development of a treatment for cystic fibrosis. It was pleasing to hear a tale of basic physiology research being conducted almost alongside clinical trials. This is the kind of story we should be publicising to engage public sympathy and understanding about animal experimentation. Far from being intimidated by such a good lecture, the rest of the talks proceeded well, on subjects ranging from regulation of peptide uptake to detection of receptors for autosomal dominant kidney disease. I was very impressed not only with the content of the communications, but also with the delivery which would have put many a lecturer to shame. This was particularly commendable to those who were presenting for the first time, which accounted for a large percentage of the attendees.

After a busy day we all retired for a bit of well-earned rest and recuperation to a local Indian restaurant. In good Physoc tradition, the wine flowed with the conversation and some of the hardier youngsters repaired to a local hostelry and then to other dens of iniquity.

The following morning the still surprisingly fresh looking group met back in the seminar room for the final session of talks. Deciding on a prize speaker was not a job I would have welcomed, but the small committee did well to choose Ms Ruth Cragg of University of Newcastle for her talk on cloning and regulation of a novel zinc transporter.

Finally after much swapping of addresses the group disbanded after lunch. All the comments about the meeting I heard and received were very positive and complimentary. These symposia are almost always well supported and attended and have a really positive function not only in increasing communication amongst young scientists but also in allowing those who are nervous a chance to present in a more informal setting than one of our larger meetings.

This YPS was unusual in that it was organised almost exclusively by one person, Giles Best. He deserves our particular thanks and congratulations for his hours of hard work, which led to this excellent meeting.

*Maggie Leggett*

# UKLSC ANIMAL SCIENCE GROUP

## Background

This group was set up in 1998 in order to coordinate effort between member Societies on the subject of the use of animals in medical research. Its membership has grown and now includes representatives of 15 Societies, as well as observers from the Research Councils, The Association of Medical Research Charities and the RDS. The ABPI are also going to be asked to observe; their active membership not being sought as the group represents academics working in universities rather than industry. The representative for The Physiological Society is Professor Bruce Matthews from the University of Bristol, and the group is very ably chaired by Professor Nancy Rothwell from the University of Manchester.

## Current Activities

Perhaps the most significant advance last year resulted from the open letter to Lord Sainsbury, regarding license applications. That letter resulted in a meeting between representatives of the group and Lord Sainsbury which should lead to other open communication with government, and has also lead already to significant positive changes.

## Review of License applications

The review of ERP and Home Office procedures is already in place. The government targets are to have a maximum time of 7 weeks for a license to be with the Home Office, and 3 weeks with ERP. This time is exclusive of time taken by the applicant for instance for amendment, although this is recognized as an area for concern as 50-60% of licenses are referred back to the applicant. Training for license preparation present problems owing to the individual nature of research, and also of local HO Inspectors. These reviews could lead to major advances in the time taken for obtaining a license. However, it is vital that institutions continue (or begin) to monitor the length of each particular stage so that the success of these processes can be measured. If you are unsure if your institution keeps such records, please ask the appropriate person, and equally if you apply for a license yourself keep your own records. I would be very pleased to hear of any particular problems, or any notable change in efficiency.

## Security

At a meeting between Mike O'Brien, representatives of the police force, scientists and anti-vivisectionists it was decided that the current legislation was sufficient for dealing with the current level of problems encountered. Regarding the freedom of information act, Universities will be treated as public bodies and will thus be subject to questions concerning public interest, i.e., if information is withheld on almost any grounds then there can be a request to ask if it is more in the public interest to release or withhold the information.

## BA Festival of Science at Glasgow University, September 3-7

As many of you are aware, The Society is running a workshop at the BA Festival on From Basic Physiology to Understanding Disease. This workshop will take place on the 7th September, and more details will be available on the website. In addition, Brian Furman is organizing a session on the Use of Animals in Research, at which Professor Rothwell among others is speaking. The BA always attracts a lot of media attention, and please do support both our session and theirs if possible.

*Maggie Leggett*

## IN-VIVO TRAINING COURSES

Many universities have either drastically reduced or abandoned teaching in-vivo practical skills. This has happened for a variety of reasons, including cost and the difficulty of obtaining teaching licenses. It has resulted in a shortage of appropriately trained applicants for PhD studentships and industry posts that require these skills. In order to address this, The Society, in conjunction with the British Pharmacological Society, are organising in-vivo training courses. These will occur in the summer vacation, lasting 6 or 7 days, and will be suitable for students between their penultimate and final year. The first two of these will run in the summer of 2002, and we hope in the future to expand the number of courses available. Students will need to attend a module 1 training course in the Easter vacation, and thus applications will have to be made at the beginning of the students' penultimate year. The courses will be assessed and accredited, and places will be competitive. There will be a nominal charge. More details will be circulated to Heads of Departments shortly.

*Maggie Leggett*

## WHITHER PHYSIOLOGY?

Many of you will know that Godfrey Smith (Glasgow) instigated a survey of members which was aimed to investigate the conditions under which people were currently working. An interim report was given by Godfrey at a meeting convened during the Kings meeting in December (a follow up from the meeting just over a year earlier in Glasgow). As traditional departments disappear in favour of larger 'divisions' – organized for reasons that are often not necessarily congruent with the convenience of scientists – some members have found themselves in new working environments, well away from others in similar fields. For some this reorganization is useful, allowing easier collaboration and more integration. However, there are definitely questions to be addressed – for many now the 'Head of Department' is not a physiologist which may impede communication – and that physiology, as a term, is disappearing from postgraduate programmes of study. Where does this leave the discipline? Is it merely a change of name, or is it indicative of something more sinister?

The American Physiological Society run a yearly survey of their membership, containing questions like this, but also more personal questions about salary and laboratory space. This may be useful for us in the future, as the answers could provide both useful centralized data as well as a bargaining tool for individuals.

Godfrey agreed that following a final reminder to members to take part in the survey, the results and a report would be available on the website. If this is well received, you can expect an improved survey next year.

*Maggie Leggett*

# NEW GOVERNANCE PROPOSALS ACCEPTED BY A RESOUNDING MAJORITY

Regular readers will have followed the progress of the Society's Governance Review over the past two years, which culminated in detailed proposals being sent to all Members in the Autumn, and an Extraordinary General Meeting at Kings College on 20 December 2000. In the month before the meeting, proxy forms sent in the approved envelopes arrived at the Society in noticeably large numbers. In fact, by the closing date two days before the meeting more than 400 had been received, but, tantalisingly, remained unopened until the day of the meeting. We knew that far more Members had responded to this issue than was usual in Society ballots but had no means of knowing which way they were voting.

The EGM attracted a larger audience than we usually see at Annual General Meetings, even though the timing meant that those attending missed lunch. Chaired by Richard Boyd, and with Chris Fry introducing the one item on the Agenda and dealing with the questions, discussion was lively and probing. Concerns centred around whether the Society really needed to have a President, and if it did, how he or she was to be chosen.

Other issues were also discussed in a similarly critical light, including the reduction in 'reserved places' on the Council, in particular the ending of automatic representation for Experimental Physiology.

After 45 minutes of discussion, members present at the meeting were asked to vote on the resolutions. The meeting was closed, with the promise to post the result of the ballot and the proxies on a notice board in the hall and Scrutineers, Paul Fraser and Dafydd Walters retired to count votes.

## Results of the Ballot on Special and Ordinary Resolutions to amend the Articles of Association and the Domestic Rules

Special Resolution 1 That the trustee/director body currently known as 'the Committee' shall be renamed 'The Council' and comprise

- 20 members nominated by and elected by the Membership of the Society,
- 5 members nominated by the Council and elected by the Membership,
- 1 member elected by the Editorial Board of the Journal of Physiology, and
- a President of the Society, elected by the Council.

***Result:*** *Carried*
***Total Votes Cast:*** *475*
***In Favour:*** *460*

**Special Resolution 2** That the Council shall elect, from amongst its members, an 'Executive Committee' of no fewer than 7 Members of the Council, five of whom will hold office as the Chairman of the Executive Committee, the Deputy Chairman of the Executive Committee, the Treasurer, the Meetings Secretary and the International Secretary respectively, together with the President and the Member of the Council elected by the Editorial Board of The Journal of Physiology.

***Result:*** *Carried*
***Total Votes Cast:*** *475*
***In Favour:*** *460*

**Special Resolution 3** That the Articles of Association be amended to incorporate all other deletions, amendments, insertions and substitutions proposed by the Committee as are necessary to accord with the above Resolutions, and that the Treasurer be authorised to prepare a revised and renumbered copy of the Society's Articles incorporating all amendments to the grammar, spelling, punctuation, layout and updated references to The Companies Act as are necessary to ensure accordance with current legal requirements, clarity, coherence and internal

consistency, for submission to the Registrar of Companies, the Inland Revenue, the Charity Commission, the Society's Bankers and Auditors and such other bodies as are entitled to receive a copy.

***Result:*** *Carried*
***Total Votes Cast:*** *475*
***In Favour:*** *459*

**Ordinary Resolution 1** That the rules governing the election of the Council and the Editorial Boards of the Society be as set out in Draft Domestic Rule C1 and C2 circulated to Members

***Result:*** *Carried*
***Total Votes Cast:*** *475*
***In Favour:*** *463*

**Ordinary Resolution 2** That the Domestic Rules be amended to incorporate all other deletions, amendments, insertions and substitutions proposed by the Committee to include amendments to the grammar, spelling, punctuation, and layout as are necessary to accord with the above Resolutions and thus allow clarity, coherence and internal consistency and that the Treasurer be authorised to prepare a revised and renumbered copy of the Society's Domestic Rules.

***Result:*** *Carried*
***Total Votes Cast:*** *475*
***In Favour:*** *461*

## Comment

The result was special in several ways. First, the size of the majority at 96% gives a clear mandate to progress. But also significant was the absolute number of members voting: 25% of the total membership – which is high for a ballot of this kind. And although we do not have exact figures, noticeable numbers of our newly enfranchised members overseas, who as foreign members did not have the right to vote until last year, took the trouble to respond.

## What Happens Now?

The new structure will be introduced at the AGM at Bristol this coming September. The current Committee has agreed transitional arrangements to ensure continuity from the 'old' system while moving to the new structure as quickly as possible.

## New Members on the Council

There will be 5 vacancies (or more, if any of those eligible to stand for re-election drop out) in the group of Members of the Council 'nominated by the Membership and elected by the Membership'. A formal request for nominations will be circulated to Members separately but you should start thinking now about nominating someone you know, or considering whether you are prepared to stand.

## What will it involve?

Members of the Council are Trustees of the Society and Directors of the Charitable Company – with the responsibilities that such a role brings.

In practical terms, members of the Council can expect to attend Council Meetings (2 or perhaps 3 per year) and serve on at least one other 'sub-committee' or group involved in the work of the Society. This gives members a chance to pursue a particular interest: be it through UK Higher Education or support for careers, or more practical matters such as the assessment of applications for grants or membership. Trustees may also be invited to serve in a further capacity on outside bodies, representing the views of the Society on or helping to organise joint activities. Service on the Council will give members a chance to influence the future of Physiology as well as the Society.

Trustees serve in an unpaid capacity, but travel and other direct expenses are reimbursed in line with current rates.

If you are considering standing for election, you may wish to talk to Chris Fry (current Committee Secretary), or any other member of the current committee to see what the job entails.

### A New Role for Affiliates

The new structure reserves two places for Affiliates on the Council. This is a new development for the Society, so there are two places to be filled. Although unable to vote formally or act as a Trustee, Affiliates on the Council will be able to take a full part in the decision making process and influence the development of the Society. The time commitment and opportunity to pursue particular interests will be similar to any other member of the Council and again, direct expenses will be reimbursed.

Full details of the process for electing Affiliates will be sent out shortly. But now is the time to consider whether you, or someone you know, should stand for election. Apart from the opportunity to influence the future of your discipline, think of all the people you will meet and the networking opportunities!

### Other places on the Council

Five places are reserved for 'Council Nominees' and information about these nominees will be provided nearer the time. The representative of the Editorial Board of the Journal of Physiology will be nominated by the Board shortly, and, again, details will be circulated to all members in due course.

*Mary Lewis*
*Executive Secretary*

## LIFE SCIENCES DIRECTORY

During 2000, we circulated all our members to ask you to check the details on our database. Lots of corrections were received and we appreciate the time many of you took to respond. Part of that exercise was to see how members would feel about having their details included in The Life Sciences Directory – a combined Membership Directory for Societies from the UK Life Sciences Committee. The first Life Sciences Directory was published at the end of 1999, without the Society. This time, the Society will take part **but only those Members who ticked the box agreeing to their details being included will be listed.**

Publication is planned for October, but such is the complexity of the exercise, address details will have been sent to Portland Press (a subsidiary of the Biochemical Society) who are producing the book by the time you read this piece. Only those who are included in the Directory will be sent a copy.

# INTERCALATED BSc BURSARIES

The Society has agreed to make an allocation (£24,000 for 2001/2002) for the support of medical, dental and veterinary students who wish to intercalate a BSc containing a strong element of physiology and including an experimental physiology research project.

## Eligibility

British medical, dental and veterinary students studying in the British Isles, intercalating a BSc within the UK who have no government, LEA or other external support for the intercalated year(s).

## Awards

Up to £2,000.

## Applications

The deadlines are June 30th and November 30th. Applications should be submitted by the Head of Department of Physiology (or equivalent) in the intercalating host department, following an internal selection process by a properly constituted committee to ensure lack of bias. No more than two applications may be submitted from an institution.

## Evaluation

Completed applications will be circulated to all members of The Physiological Society's Grants Sub-Committee, whose scoring will determine funding. When an institution submits more than one application, the Head of Physiology (or equivalent) will be asked to rank those applicants, although that information will count only as a reference point and will not be binding on the Sub-Committee. Assessment will take into account academic ability, research potential, and financial need, and the details of the research project proposed.

Please complete the application form on pages 39/40.

Further application forms are available from
The Administrator (BSc Bursaries)
The Physiological Society
PO Box 11319, LONDON WC1E 7JF
or may be downloaded from the web.

Tel (020) 7631 1459
Email: jgould@physiology.demon.co.uk
Web site: http://www.physoc.org

# CELLULAR SIGNALLING SPECIAL INTEREST GROUP

Over the past 2 years or so, we have found that most abstracts submitted for presentation for the Molecular Physiology SIG have been on a theme of cell control and/or signal transduction mechanisms. We have also noted that abstracts related to the control of intracellular $Ca^{2+}$ homeostasis do not easily fit within any of the established SIGs (although many abstracts are submitted to the Ion Channels section). Since this has resulted in the *ad hoc* appearance of Cellular Signalling and $Ca^{2+}$ Signalling designated sessions at Meetings, we have decided to replace Molecular Physiology with a new SIG – Cellular Signalling. The remit of this group is to promote an advanced understanding of signal transduction and cell control mechanisms through designated communications, lectures and symposia. As $Ca^{2+}$ signalling in the context of physiological control mechanisms is one example of the type of activity that this SIG will seek to promote, Drs Martin Bootman and Peter Lipp have kindly agreed to be the first convenors of Cellular Signalling. In order to develop networks of communications with members who have interests in the field of cell control, we would like to establish a database of contact details. If you would like to be added to an email distribution list established for the SIG, would you please email James Relf at the London office of the Physiological Society (jrelf@physoc.org) with you name, postal address and contact email. Designated sessions for Cellular Signalling have been entered into the scientific programme for the Bristol and York Meetings of the Society this year.

**Cellular Signalling SIG contact details:**

Dr M. Bootman
Laboratory of Molecular Signalling
The Babraham Institute
Babraham, Cambridge CB2 4AT
Tel: (01223) 496 515
Fax: (01223) 496 033
Email: martin.bootman@bbsrc.ac.uk

Dr P. Lipp
Laboratory of Molecular Signalling
The Babraham Institute
Babraham, Cambridge CB2 4AT
Tel: (01223) 496 515
Fax: (01223) 496 033
Email: peter.lipp@bbsrc.ac.uk

# JAMES ALEXANDER BARCLAY

James (Jimmy) Alexander Barclay was born in Milltown Campfield in the parish of Kincardine O'Neil in Aberdeenshire on December 19th 1909. He was the second youngest and only boy of four children. His parents were farmers, who were not wealthy. However, with the aid of financial support from The Carnegie Trust, Jimmy was able to enter Aberdeen University in 1925-6, only to find that he was too young to study Medicine. He took an MA in Classics, and at this time considered entering the church. Times were hard whilst at Aberdeen, and Jimmy supplemented his income by beating for the royal shoots on the Balmoral estate. This activity provided meals, a little extra money, and a ready supply of glow-worms to provide illumination for his evening studies!

After his MA, Jimmy remained in Aberdeen and studied Medicine including an intercalated BSc in Physiology. He graduated in 1937, and moved south to Leeds where he found employment in various locum positions. Here, he met and married Grizel Borthwick, a bacteriologist. Soon after, they both moved to Birmingham and to the University, where Jimmy entered the Department of Physiology then headed by Professor Guilding. Jimmy remained in the department for the whole of his professional career, and became a Reader in renal physiology. He also completed a spell as acting Head of Department. Jimmy belonged very much to the generation of "classical" whole animal renal physiologists. His research centred on mechanisms of acid secretion by the kidney. In later years, in collaboration with the biochemists, Ken White and Michael Hickling his work shifted to concentrate on isolation of sodium-binding polypeptides from erythrocytes and cardiac muscle. In 1967, together with White, he published a successful monograph entitled "Elementary Calculations in Physiology & Biochemistry", written, said Jimmy to address the "lamentable innumeracy" of students in the life sciences. He retired in 1973.

Following Grizel's death in 1991, Jimmy moved to Bath to be closer to his family. In 1997 he married for a second time. His second wife, Beryl, a devout Christian and retired nurse, owned a car, which was especially useful in conveying the now poorly-sighted Jimmy on daily "quality control" missions to various hostelries in the Bath and Avon area on behalf of CAMRA, of which he was one of the early members.

Jimmy died just two weeks short of his ninetieth birthday in 1999. He was an extremely colourful character, who lived life to the full. He did not suffer fools gladly, and could display an acerbic manner with people he considered so to be. However, he was also capable of the greatest warmth and generosity to students and co-workers alike. He is survived by Beryl, and by his two sons Bruce and Donald from his first marriage.

*Stan White*
*Department of Biomedical Sciences*
*University of Sheffield*

# TAKIS ANAGNOSTOPOULOS

Takis Anagnostopoulos, research director in INSERM, the French medical research institute, and previous Head of a renal physiology research unit in Paris, died on November 6, 2000 at the age of 64. Born in Patras, Greece, he left his country at the age of 17 to pursue medical studies in Montpelier, in the south of France. After becoming an Intern in Paris hospitals, his discovery of basic research in the laboratory of Professor Pierre Royer in the paediatric service of Necker Hospital for Sick Children definitively changed the orientation of the rest of his professional life. He dedicated himself to renal physiology, especially to ion transport in the nephron. For training in these techniques, he went to the United States for three years, first to the laboratories of Dr. Watson and Dr. Bentzel in Buffalo and then to the labs of Dr. Pitts and Dr. Windhager in New York City where he picked up the techniques of *in vivo* micropuncture and, especially, electrophysiology, which became his preferred technique. Upon his return to Paris, he created the first French laboratory of renal electrophysiology while simultaneously continuing his training in the lab of Prof. Edouard Coraboeuf, director of the laboratory of cardiac electrophysiology at the University of Orsay.

His laboratory, created originally with his faithful technician Micheline Bouthier, also tragically deceased at the end of last year, developed rapidly during the 80's within the INSERM Unit directed by Dr. Renée Habib at the Necker Hospital for Sick Children. Throughout this period, Takis participated with energy and even combativeness in the controversies and progress of the field. He was among the first to measure transepithelial and transmembrane electric potentials in the nephron, he developed an original mathematical analysis which, by considering the renal tube as a system of two concentric electrical cables, allowed determination of the full set of resistance parameters of the tubular epithelium, and he recognised very early the importance of anion exchange in renal transport.

Doctor of Medicine and Docteur ès Sciences, he was also a teacher in three Paris universities and promoted, as early as the 1970s, a modernisation of medical and biological curricula to keep up with the fantastic progress of biological knowledge. Throughout his scientific career, he manifested intellectual rigor, clarity, and enthusiasm. From day to day, we appreciated his tolerant spirit, his simplicity, and his friendship towards all those who worked with him.

Outside his scientific activities, he liked nothing better than to join his "buddies" at the Orsay soccer club, and it was clear that being able to discuss soccer counted for a lot if you were a member of his laboratory. His other passion was, of course, Greece. Although he was completely integrated in his adopted country, which was also that of his children and his professional success, nonetheless, as he grew older, the nostalgia for Greece, perhaps for his youth, became more present, and he loved to return to his mother country as often as possible.

So, Takis has left us, but we hold the memory of an eternal smiling youth full of life.

*Aleksander Edelman, Gabrielle Planelles, Jacques Teulon & S Randall Thomas*

# Joint meeting with the German Physiological Society
# Tübingen
# 15 – 19 March 2002

## *Physiological Society Travel Grant Application Form*

PLEASE COMPLETE IN CAPITALS

Surname

Title and forenames

Work address

Email

Work tel

Fax

**Membership of The Physiological Society**
(please tick one box)

Member ☐

Affiliate ☐

Candidate for membership ☐

Membership number

Funds are available towards the costs of physiologists wishing to attend the meeting to present their work. The sum available is variable, but it is hoped to be in the region of £150 to £200. Applicants should also pursue other sources of funding.

**Details of employment or status**
(please tick boxes as appropriate)

Appointment/status

Employer/funding body

Member of UK/Irish department of Physiology or related sciences ☐

Graduate ☐

Post doctorate worker ☐

Academic staff member ☐

Technical staff member ☐

Visitor ☐

NHS clinician not part of a medical school ☐

Member of MRC, other UK research institute or equivalent ☐

Other employment (please provide details)

**At the meeting:**

Do you intend to submit – a poster? yes/no

– an oral communication? yes/no

– a demonstration? yes/no

Title of abstract

**Funding**
Funding applied for from the Society

£

*(note each application will be considered individually and funds are limited)*

**Other sources of funds**
Please give details of other bodies to which you have applied or intend to apply for support, including maximum award and date of notification.

Signed

Date

Signature of Head of Department confirming eligibility if not a member or affiliate

Signed

Name

**Deadline for receipts of applications: 28 September 2001**

Submit six (6) copies of this form to
James Relf, Membership Administrator,
The Physiological Society,
PO Box 11319, London WC1E 7JF

PLEASE TURN OVER ›

## *Physiological Society Travel Grant Application Form cont'd*

Summary of abstract: please give, in not more than 250 words, on the paper or poster you plan to present at the meeting, including co-authors. Give the name of the presenter.

Note here any additional scientific purposes for your visit to Germany: e.g. attendance at other meetings, visits to laboratories, collaborations etc. Please supply copies of supporting documents, such as invitations, where relevant.

If you are awarded a grant we would like to transfer the funds directly into your bank/building society account. Please complete the following:

Bank/Building Society

Name of account holder(s)

Account number ☐☐☐☐☐☐☐☐ Sort code ☐☐-☐☐-☐☐

# APPLICATION FOR INTERCALATED BSc BURSARY

***Please type***

**Applicant's details**

Name _____ Date of birth _____

Address _____

_____

_____

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)

_____

_____

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PLEASE TURN OVER ›

# APPLICATION FOR INTERCALATED BSc BURSARY

***continued***

**Previous Studies and Relevant Work Experience**

A Levels/Highers Subject Year Grade

University Degree Subject

Institution

Course subjects/grades

Year 1

Year 2

Year 3

Details of any special projects/outstanding achievements

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

Address

Tel

2. Name Position

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 ☐☐☐☐☐☐☐☐

Name of account holder Sort code ☐☐-☐☐-☐☐

On completion, the first referee should return **SIX COPIES** of this form and of supporting documenta-tion to The Administrator (BSc Bursaries), The Physiological Society, PO Box 11319, LONDON WC1E 7JF. **Closing dates June 30th and November 30th.**

*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 Autumn 2001 edition should reach the* ***Administration Office by 7 May****.*

## TECHNIQUES WORKSHOPS 2001

There will be three techniques workshops this year. Further information will be circulated and will also be in available on the website, but queries can be forwarded to Maggie Leggett at mleggett@physiology.demon.co.uk
Equally prospective bids to host workshops for 2002 should in the first instance be forwarded to Maggie Leggett.

**Confirmed workshops include:**

University of Glasgow, Workshop on Fluorescence Imaging Using Confocal Microscopy, September/October 2001 (details to follow)

University of Bristol, Teaching Symposium on "Dynamic confocal imaging of living brain", 30 June 2001. Organisers: Drs. S. Kasparov and J.F.R. Paton

This symposium will bring together the leading international experts in confocal imaging of cells within living brain slices and/or in situ brain preparations. Three main topics will be of particular interest: 1) motility of nerve cells, 2) use of fluorescence resonance energy transfer (FRET) in real-time imaging 3) advances in two-photon imaging in integrative preparations. Not more than 8 talks (preferably 6) of 30 – 35 minutes each will be presented and demonstrations will be organized during the lunch break.

Further, we will encourage other members of the Bristol Imaging Group to present their data and take part in the discussions. Proposed list of speakers and their topics:

**USA:**

**1** Yuste, R. Motility of neurites in living brain slices. Department of Pathology, Columbia University, College of Physicians and Surgeons, 630 West 168th Street, New York, NY 10032; United States.

**2** G.Y. Fan – Two-photon imaging using cameleons Dr. G.Y. Fan, Microscopy/ Imaging Res. Natl. Ctr., Department of Neurosciences, University of California, San Diego, CA 92093; United States.

**3** K. Svoboda Experience-dependent plasticity of dendritic spines in the developing rat barrel cortex in vivo Cold Spring Harbor Laboratory, 1 Bungtown Rd, Cold Spring Harbor, NY 11724; United States.

**Europe:**

**4** A. Konnerth. NMDA mediated Ca signals. TU Munchen, Institut fur Physiologie, 80802 Munchen; Germany.

**5** T. Bonhoeffer (or F. Engert). LTP-related dendritic spine changes. Max-Planck Institute of Neurobiology, Am Klopferspitz 18A, 82152 Munchen-Martinsried; Germany

**UK:**

**6** Blakemore C. Morphology and growth patterns of developing thalamocortical axons. University Laboratory of Physiology, University of Oxford, Parks Road, Oxford OX1 3PT; United Kingdom.

**7** Kasparov S. / Paton J.F.R. – Bristol. Understanding physiology of the NTS using FRET fusion proteins.

**8** A talk from Leica. Advancements in confocal imaging in living tissue (and novel fluorophores?).

**Other potential speakers:**

J.E. Lisman, Volen Center for Complex Systems, Brandeis University, Waltham, MA 02254; United States. A role of actin filament in synaptic transmission and long-term potentiation.

K. Krnjevic, McIntyre Centre, 3655 Drummond St., Montreal, Que. H3G 1Y6; Canada. Intraneuronal [$Ca^{2+}$] changes induced by 2-deoxy-D-glucose in rat hippocampal slices**

**********

## YOUNG PHYSIOLOGIST'S SYMPOSIA 2001

There will be two Young Physiologist's Symposia in 2001. Further information will be circulated and will also be in available on the website, but queries can be forwarded to Maggie Leggett at mleggett@physiology.demon.co.uk.
Equally, prospective bids to host symposia for 2002 should in the first instance be forwarded to Maggie Leggett.

**Symposia for 2001:**

***University of Cambridge***
"Sensational Physiology" 24-25 September 2001. Details available from Society website.

**********

**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**

**********

Jacques Duysens and Herman Kingma kindly invite you to:

## ISPG 2001

## June 23-27th 2001

**Symposium of the International Society for Postural and Gait Research**

**CONTROL OF POSTURE AND GAIT**

Website:
http://www.mbfys.kun.nl/ispg2001

Second Announcement and Call for Papers

Congress to be held at
MAASTRICHT, The Netherlands

**Organised by:**

***Herman Kingma, PhD***
Division of Balance Disorders Research:
Maastricht Research Institute Brain & behaviour
Health care:
Dept. of ORL and Head and Neck Surgery
University Hospital Maastricht
E-Mail: H.Kingma@kno.azm.nl
*and*
***Jacques Duysens, MD, PhD***
Dept. of Medical Physics and Biophysics
University of Nijmegen, KUN
jaak@mbfys.kun.nl
Health care: SMK-research
Sint Maartenskliniek, Nijmegen, The Netherlands
E-Mail: j.duysens@smk-research.nl

**Themes**

- Falls in the elderly
- Cognitive loading in posture and gait
- Development of posture and gait
- Robotics and models

- Gait navigation
- Central Pattern Generators and their control
- Interlimb coordination
- Neuro-imaging of gait and posture
- Anticipatory postural control
- Pathology: Parkinson and cerebellum
- Gait and posture in stroke
- CP and Botulinum toxin
- Gait and posture in microgravity
- Gait and posture training programs
- Rehabilitation of gait and posture
- Orthopaedic aspects
- Perturbations of gait and posture
- Vestibular aspects of posture and gait
- Spinal lesion
- Vision and Posture & Gait

**Workshops on**

- EMG
- Force measurements
- 3-D motion analysis
- Rehabilitation technology

The final program of the parallel sessions will be arranged in accordance with the registered number of speakers and participants

## PROCEEDINGS AND PUBLICATIONS

**Congress book**

As in former versions of the congress, all participants (oral sessions and posters) are entitled to submit a 4-page paper. This paper will be the basis for selection of some of the oral presentations. Normally these papers will be included in the book but a reviewing process will be used to screen for papers which have to be revised or even excluded. The book will be published by NPI with ISBN registration. This book will be handed out to all registered participants at the meeting.

**Submission of papers**

Prospective participants are requested to E-mail a draft paper in either WORD or WORDPERFECT (maximum 1200 words, including 1 or 2 illustrations; without illustrations the maximum is 1280 words). All participants should send their paper to

cal.conferenceagency@wxs.nl

for review by the International Program Committee. All submissions must be written in English, starting with a succinct statement of the problem, the results achieved, their significance and a comparison with previous work. The following sections should be present: title, authors with affiliation and addresses, introduction, methods, results, discussion, references. The format for these papers is the same as for the papers for the "Posture and Gait" journal except that a summary abstract is not needed and that there is a strict limitation of number of words. If photographs are used for illustrations the authors should provide an original. For examples for the 4 page papers one can also consult the books from previous meetings of ISPG.

The submission should also include a cover sheet with:

- Preferred format:
  Oral or Poster presentation
- Name of author to contact for correspondence
- E-mail address, tel. # and fax # of contact author
- Topics which best describe the paper (max. 5 keywords)
- Theme of session or workshop

**Important dates:**

- December 15th ,2000: Submission deadline for papers
- February 1st, 2001: Notification of acceptance; possibly advise for adjustments
- March 1st 2OOl: Delivery of adjusted papers
- June 23-27th: ISPG2OO1 congress

## SESSIONS

**Oral presentations**

There are both invited speakers and free oral presentations. Those wishing to present an oral paper should indicate their choice when sending their paper. On the basis of the papers a selection will be made for oral presentations. A limited number of speakers will be invited for plenary lectures.

**Poster presentations**

Poster presentations are encouraged for people who wish to receive peer feedback. The papers based on the posters can besubmitted for inclusion in the book. Format instructions for the poster will follow.

**Congress Language**

The official conference language is English. No simultaneous translation service will be provided.

## CONGRESS LOCATION

**Address:**

Crowne Plaza Hotel Maastricht
Ruiterij 1
6221 EW Maastricht
The Netherlands

Telephone: +31 (0) 43 350 91 91
Telefax: +31 (0) 43 350 91 92
E-mail address:
cpmaastricht@bilderberg.nl
http://www.crowneplaza.com/

**Maastricht, Congress Site**

Situated close to the borders of Belgium and Germany, the Roman city of Maastricht has a cosmopolitan atmosphere. It is the capital of the province "Limburg" in the southernmost part of the Netherlands. To visit Maastricht is like traveling through time. Walk on Roman cobble stones from 150 BC and visit the halls where the Maastricht Treaty was signed in 1992. Enjoy Maastricht"s skyline of church's spires and towers and its tree lined squares. But also be sure not to miss 'In den Ouden Vogelstruys', the Netherlands' oldest pub. We guarantee that Maastricht and its people will delight and charm you.

## REGISTRATION

See our website for instructions:
http://www.mbfys.kun.nl/ispg2001

*Organising Secretariat*

Conference Agency Limburg
P.O. Box 1402
6201 BK Maastricht
The Netherlands

Telephone: +31(0)43 361 91 92
Telefax: +31(0)43 361 90 20
E-mail address:
cal.conferenceagency@wxs.nl**

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## SIGNALLING HOMEOSTASIS Biochemical Society Meeting at Trinity College, Dublin 11 – 13 July 2001

Signalling between cells is the major topic to be discussed at this summer meeting organised by the Biochemical Society

taking place at Trinity College Dublin from 11 to 13 July 2001.

**The Scientific Programme will be covering:**

- DNA Damage Signalling and Apoptosis
- Neurotransmitter Transporters: Molecular Mechanism and Regulation (vital components for transmission of nerve impulses)
- Mitochondrial Uncoupling Proteins (converting your energy into heat instead of laying down flesh!)
- Signal Transduction During Innate and Adaptive Immunity
- Teaching Practical Skills to 21st Century Biochemists
- Enzymes That Regulate Lipid Metabolism in Cell Signalling

The Biochemical Society's first meeting of the real new millennium includes over 80 speakers from 20 countries. They will be presenting their papers in a three-day programme, including two medal lectures.

**Medal winning speakers:**

Stuart Ferguson – *Keilin's cytochromes: how bacteria vary them, use them and make them*

Prof. Kingston H.G. Mills

**Key speakers include:**

Stephen Jackson *(Cambridge)*
Jan Hoeijmakers *(Netherlands)*
Yossi Shiloh *(Israel)*
Gerard Evans *(San Francisco)*
David Nicholls *(California)*
Martin Brand *(Cambridge, UK)*
Martin Klingenberg *(Germany)*
Keith Garlid *(Beaverton, USA)*
Doreen Cantrell *(ICRF)*
Professor Luke O'Neill *(Dublin)*
J. Hoffmann *(Strasbourg, France)*
Peter Parker *(ICRF, UK)*
Dario Alessi *(Dundee)*
Hans Bos *(Utrecht)*
David Brindley *(Canada)*
Sarah Speigel *(DC, USA)*
Phil Hawkins *(Babraham Institute)*
C. Peter Downes *(Dundee)*
Tomohiro Kurosaki *(Japan)*

**Best Poster Prize**

The Biochemical Society will award £200 for the best student poster displayed at the meeting and £50 for the runner up. The judges will consider scientific content and presentation when deciding the winner. Entrants must be a student member of the Biochemical Society.

***Poster abstract deadline:*** 16 April 2001
***Deadline for registration:*** 28 May 2001

**Delegate Registration fees**

| | |
|---|---|
| Society members | £25 for 3 days |
| Student members | FREE |
| Non-members | £100 per day |
| Press | FREE |

**Biochemical Society membership**

Join before the meeting and save £££s. Contact the Biochemical Society for details.
Membership fee: Full £47, Student £14
Travel grants are available to support both full and student members of the Biochemical Society attend this meeting.

Further details and the full programme are available on the Meeting web site:
http://www.biochemistry.org/meetings/

**Notes to Editors:**

The congress is organised by the Biochemical Society: full details are available from Meetings Office, Biochemical Society,
59 Portland Place, London W1N 3AJ
Tel: +44 (0)20 7580 5530
Fax: +44 (0)20 7323 1136

**Press information:**

Sheila Mills, Meetings Office, Biochemical Society,
59 Portland Place, London W1N 3AJ
Tel: +44 (0)20 7580 5530
Fax: +44 (0)20 7323 1136
Email: meetings@biochemistry.org.

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## ELECTRONIC SUBMISSION TO THE JOURNAL OF PHYSIOLOGY

The Journal of Physiology now accepts manuscripts submitted electronically via the World Wide Web. The submission form, together with author instructions, can be accessed from:
http://www.jphysiol.org.

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53rd Harden Conference

## 'PROTEOGLYCANS: MESSAGES IN THE MATRIX'

### St Martin's College, Ambleside, Lake District, UK

### 16 –21 August 2001

### Proteoglycans: messages in the matrix

- proteoglycans – a multidisciplinary approach
- impact on biomedicine, cell and tissue engineering
- highlighting receptor signalling and cell interactions with the extracellular matrix

**Organising Committee**

Professor John Gallagher *(Paterson Institute, Christie Hospital, Manchester)*
Professor Tim Hardingham *(University of Manchester)*
Professor Bruce Caterson *(University College of Wales, Cardiff)*

**Scientific Programme includes sessions on:**

- Glycosaminoglycan Biosynthesis
- Proteoglycans and GAGs in Development and Function
- Neurobiology
- Growth Factors and Chemokines
- Protein – GAG Interaction
- GAGs.PGs in the ECM – Organisation Turnover
- Signalling Networks
- GAG Hydrolases

**Key speakers include:**

Jeff Esko *(University of California, USA)*
Bob Rosenberg *(Massachusetts, USA)*
Kazuyuki Sugahara *(Kobe Pharmaceutical University, Japan)*
Lena Kjellen *(Biomedical Centre, Sweden)*
Ariane Agostini *(University of Geneva, Switzerland)*
Yu Yamaguchi *(Burnham Institute, USA)*
Ian Nieduszynski *(University of Lancaster, UK)*
Tony Day *(University of Oxford, UK)*
Vince Hascall *(Ohio, USA)*

Hans Kresse *(Muenster, Germany)*
Renato Iozzo *(Philadelphia, USA)*
John Couchman *(University of Alabama,Birmingham USA)*
Jorge Filmus *(Toronto, Canada)*
Guido David *(University of Leuven, Belguim)*
Israel Vlodavsky *(Jerusalem, Israel)*

**Poster Presentation**

Posters are welcomed and must be submitted online at www.biochemistry.org/meetings by 16 May 2001. Applicants intending to present a poster will be given priority

**POSTER ABSTRACT DEADLINE: 16 May 2001**

**Delegate Registration fees**

***Before 16 May 2001:*** £390 (en-suite) and £320 (standard).

***After 16 May 2001*** the fees rise to £430 (ensuite) and £360 (standard).
Fees include registration, accommodation and food for the entire meeting.
There will be a limited number of bursaries for young scientists.

**REGISTRATION DEADLINE: 16 May 2001**

Scientists wishing to participate are asked to contact The Meetings Office for an application pack at the address below. Applications should be submitted by 16 May 2001.

The Meetings Office, Biochemical Society,
59 Portland Place, London W1B 1QW
Tel: 020 7580 3481 Fax: 020 7637 7626
E-mail: meetings@biochemistry.org

Further details and the full programme are available on the Meeting web site:
http://www.biochemistry.org/meetings/

**Notes to Editors:**
The conference is organised by the Biochemical Society: full details are available from Meetings Office,
Biochemical Society,
59 Portland Place, London W1N 3AJ
Tel: +44 (0)20 7580 5530
Fax: +44 (0)20 7323 1136

**Press information:**
Sheila Mills, Meetings Office,
Biochemical Society,
59 Portland Place, London W1N 3AJ
Tel: +44 (0)20 7580 5530
Fax: +44 (0)20 7323 1136
Email: meetings@biochemistry.org*

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## STRUCTURE AND FUNCTION OF ION CHANNELS
## 2-5 September 2001

Fairmont Resort Blue Mountains, Leura, Australia.
**An official satellite of the 34th IUPS Congress**

Scientists of all disciplines with an interest in ion channels are invited to attend and participate in this exciting satellite symposium on the Structure and Function of Ion Channels.

The symposium will embrace the new ideas and challenges of ion channel research.

**Plenary Lecture**
Prof. Frances Ashcroft, Oxford University

***Invited speakers include:***

| | |
|---|---|
| Henry Lester | Walter StChmer |
| Michel Lazdunski | Boris Martinac |
| Chris Miller | Gary Housley |
| Clay Armstrong | Arthur Karlin |
| Steve Sine | Joe Lynch |
| Annette Dolphin | Karl Magleby |
| Francisco Bezanilla | David Clapham |

As an official satellite symposium of the 34th IUPS Congress you can register for this symposium when you register for the IUPS Congress, or directly with the organisers. The IUPS Congress is in Christchurch, New Zealand 26-31 August 2001.

This satellite symposium follows the Congress.

Further information can be found at the symposium website-
http:\\www.garvan.unsw.edu.au\public\Conferences\Channels**

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## MOVEMENT AND SENSATION
## Cairns Convention Centre
## 3-6 September 2001

A meeting on Movement and Sensation is to be held as an official satellite of the IUPS Congress (Christchurch, New Zealand, 26-31 August 2001). The Meeting will be held at the Cairns Convention Centre in Australia, close to the Great Barrier Reef, over the period 3-6 September. The Meeting continues a tradition of 'Motor Control' conferences held in association with IUPS. The meeting will feature keynote speakers and invited discussants covering 10 broad themes in Movement and Sensation. At least 2 poster sessions will be held. Meeting organised by Professor Uwe Proske and Professor Simon Gandevia in Australia. Further information can be obtained from: www.cairns2001.unsw.edu.au *

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## 2nd INTERNATIONAL SYMPOSIUM ON COUGH: PHARMACOLOGY AND THERAPY
## 25-27 October 2001

A symposium will be held combining both basic and clinical aspects of cough at the National Heart and LungInstitute, Imperial College, Dovehouse Street, London SW3 6LY, UK. There will be four half-day sessions, starting on the afternoon of Thursday October 25 and ending at lunchtime on Saturday October 27.

**1 Basic pharmacology of cough.** The physiology and pharmacology of airway receptors involved in cough, their interactions, and their plasticity.

**2 Basic pharmacology of cough (continued).** The central nervous physiology and pharmacology of cough, and the validity of animal models for cough.

**3 Therapy of cough: clinical needs.** The epidemiology of cough, its measurement and markers, provocation tests for cough, pediatric problems in cough treatment, and the Quality of Life of coughers.

**4. Therapy of cough: active agents.** Centrally and peripherally acting antitussives, psychological factors in cough and the effectiveness of placebos, the voluntary control of cough, and the use of protussive and mucoactive agents.

*continued...*

Posters and short papers are invited.

Further information, a provisional programme and an application form can be obtained from the organizers:

***John Widdicombe***
Dept. of Human Physiology and Aerospace Medicine
GKT School of Biomedical Sciences
Shepherds's House
Guy's Campus
London Bridge
London SE1 9RT, UK*

Tel: 020 8947 6614
Fax: 020 8286 1815
E-mail: JohnWiddicombeJ@aol.com

***K. Fan Chung***
Imperial College
National Heart and Lung Institute
Dovehouse Street
London SW3 6LY, UK

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## MOLECULAR TECHNIQUES WORKSHOP 2002

### University College, Cork

For the past five years, the Physiological Society and the Wellcome Trust have sponsored the Molecular Techniques Workshop at the University of Glasgow. More than 70 post-doctoral scientists and final year PhD students have attended the course. Initiated in 1996 by Professor Janet Allen, the course provided training in a range of practical and theoretical molecular techniques. The course was significantly revised in 1999 by Professor Rod Dimaline, (University of Liverpool), Dr. Stan White (University of Sheffield) and Dr. Patrick Harrison (University of Glasgow), and was held for a further two years at the University of Glasgow (1999 and 2000). Following the recent move of Dr. Harrison to the Cellular Physiology Research Unit in the Department of Physiology at University College, Cork in Ireland, it has been agreed to hold the next workshop in Cork at Easter 2002.

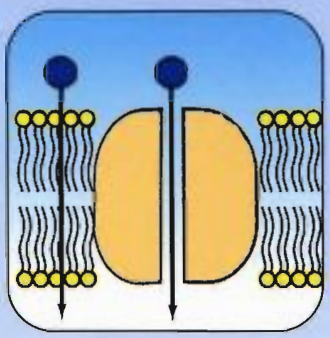
Current protocols and details of previous courses can be found at:
http://www.biochem.gla.ac.uk/MolPhysiol.html

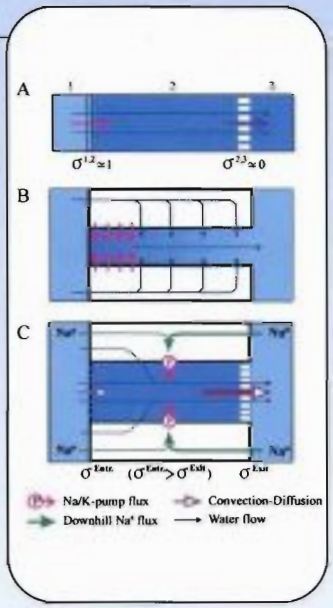
Further information about the 2002 course will be available in the Physiological Society magazine and the Society's web page http://.physoc.org, later this year. Alternatively, contact Dr. Patrick Harrison by e-mail: p.harrison@ucc.ie

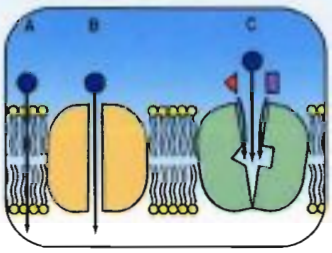
# THE JOURNAL OF PHYSIOLOGY

SYMPOSIUM

XXXIV INTERNATIONAL CONGRESS OF PHYSIOLOGICAL SCIENCES






*The Journal of Physiology Synthesium*

## Water transport controversies

**Thursday, 30 August 2001**
**Christchurch, New Zealand**

*Moderators: Luis Reuss, Barry H Hirst*

**The Journal of Physiology Distinguished Lecture**
**Peter Agre**
Johns Hopkins University, Baltimore, USA
*Aquaporins*

**Synthesium speaker**
**Walter Boron**
Yale University, New Haven, USA
*Aquaporin – a gas channel*

**Discussant**
**Alan Verkman**
University of California, San Francisco, USA

**Synthesium speaker**
**Erik H Larsen**
University of Copenhagen, Denmark
*Ion recirculation and isotonic transport*

**Discussant**
**Kenneth R Spring**
NIH, Bethesda, USA

**Synthesium speaker**
**Ernest M Wright**
University of California, Los Angeles, USA
*Water pumps*

**Discussant**
**Jean-Yves Lapointe**
University of Montreal, Quebec, Canada

**For further information go to**
www.physoc.org/symposia
or email:
JPSymposium@physoc.org

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