PHYSIOLOGYNEWS

summer 2006 | number 63

Meetings
UCL
Brazil
Manchester
Munich

Also featuring:

Trials and tribulations of self-experimentation
Alison Brading's 10 key papers
A century of physiology online
Working out aerobic fitness
Bursting with currents
Granny's going global

A publication of The Physiological Society

MANCHESTER FOCUSED MEETING

Frontiers in epithelial transport

6–7 April 2006


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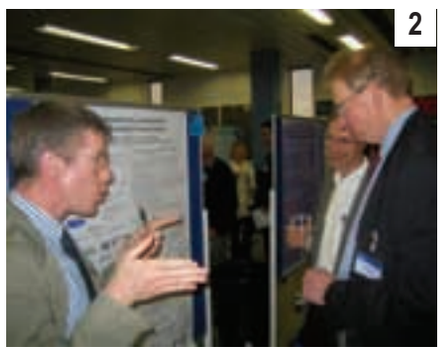
1 Welcome reception, Whitworth Art Gallery **2** David Sheppard (Bristol), left, defends his poster to Seth Alper (Harvard) and Barry Argent (Newcastle) **3** Poster session **4** Welcome reception **5** Lowry Centre entrance **6** Conference dinner at the Lowry Centre **7** The speakers **8** Poster Prize winner Jennifer Evans (Glasgow) **9** Martin Steward (Manchester), 2nd right, shares a joke with Masataka Murakami (Okazaki), 2nd left, and Hiroshi Ishiguro (Nagoya) **10** Jim Melvin (Rochester), left, and Shmuel Muallen (Dallas) **11** Speakers (from left) David Cook (Sydney), Mike Gray (Newcastle) and Karl Kunzelmann (Regensburg) **12** Craig Smith (Manchester), left, and Jeppe Praetorius (Aarhus) at the Lowry Centre gallery **13** Boarding deluxe transport to the conference dinner **14** Conference chair Maynard Case passes round the begging bowl.

(*photos by Austin Elliott, Simon Kellas and Donald Ward*)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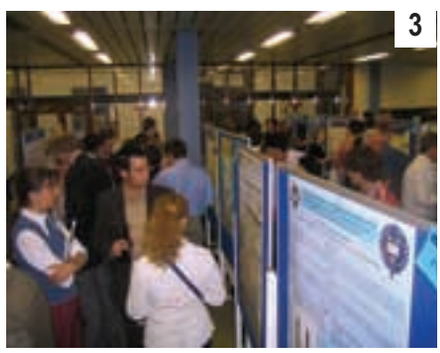
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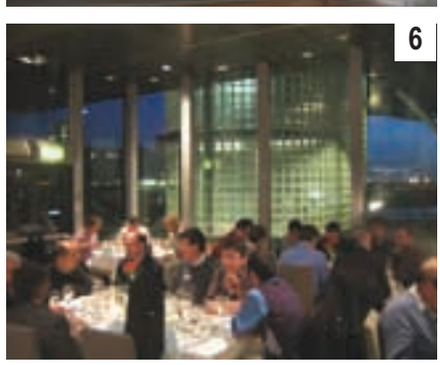
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The Society's dog. 'Rudolf Magnus gave me to Charles Sherrington, who gave me to Henry Dale, who gave me to the Physiological Society in October 1942'

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Cover photos

Front. The auto-icon of Jeremy Bentham (JB) will be welcoming you to The Physiological Society meeting at UCL in July. In the formation of UCL, JB provided financial support and much of the spirit behind the ethos of what UCL would stand for as an institution. Established in 1828 using money raised through selling shares, UCL was originally known as the University of London before being rebranded as University College London in 1836. The first University established in England after Oxford and Cambridge. It was formed by, what JB described as an 'association of liberals' and as such UCL was the first university not to discriminate on the basis of sex or faith (Source: Harte N & North J. *The world of UCL 1828-2004*).

Back. The quad, University College London

PHYSIOLOGYNEWS

Action points

Grants

For full information on Members' and Affiliates' Travel Grants, Network Interaction Grants, Non-Society Symposia Grants, Vacation Studentship Scheme, Departmental Seminar Scheme, Centres of Excellence and Junior Fellowships visit: http://www.physoc.org/grants

Membership applications

Applications for Full and Affiliate Membership are received throughout the year and have no deadlines. A decision is normally made within 7 days of the Administration Office receiving the application. For full details please visit: http://www.physoc.org/join

Change of address

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

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

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Physiology News

Deadlines

Letters and articles and all other contributions for inclusion in the Autumn 2006 issue, No. 64, should reach the Publications Office (lrimmer@physoc.org) by 30 June 2006. Short news items are encouraged and can usually be included as late copy if space permits.

Suggestions for articles

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

Physiology News Online

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

Guidelines for contributors

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

Format of articles

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

Length of articles

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

Submission of articles

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

Illustrations and authors' photographs

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

References

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

In this issue

Welcome to the Summer 2006 edition of *Physiology News*, with our usual mix of features. The scientific articles range from molecules to man (to borrow a phrase), including Alison Brading's 10 key papers (p. 9) , and a jaw-dropping account from Hugh de Wardener of the kind of experiments a physiologist could carry out on himself back in the days before ethics committees (p 13).

We also report on a couple of notable announcements. Firstly, The Physiological Society has a new Chief Executive and a new President-Elect (p. 44), and secondly the full back-catalogue of The Society's journals (right back to 1878) is now live online (p. 40).

Eagle-eyed readers may spot that this issue is missing our regular diary feature *A Week in the Life*. I am sad about this, as a diary has appeared in every issue since Alan North kicked off the feature in PN 55 (Summer 2004). But we had no volunteers this time, and we finally seem to have run out of people that the editorial team have enough incriminating material on to 'persuade' them to become diarists. However, every threat is another opportunity (©your head of department), so any would-be diarists out there, get writing. Why not keep a diary of your next conference trip? Or a week of exam season hell? Otherwise I might have to write the next one myself.

Austin Elliott

Oi, ref!
Unbelievable! (p. 46)

Scientists needed

It is a mark of many scientists I know that they attribute their interest in science to two things in their childhood. One is inquisitiveness – posing the question 'why?' The other is early exposure to the idea that you could sometimes find out why by looking at things closely – observation – and/or doing experiments – 'what if?' This insight into experiment as the source of scientific knowledge may come from an inspired teacher, from family members, or even from a book, but without it science will always seem like magic. With it, it can be recognised correctly as a result of collective endeavour, thought, and imagination.

Everyone, from governments and employers through to learned societies, agrees we need more science and technology-literate citizens. The National Curriculum in the UK repeatedly stresses the need for pupils to be taught to appreciate that the scientific facts they learn are based on evidence derived from experimentation. And experiments have other benefits, too: aiding learning – 'seeing is believing' – and keeping pupils interested by making schoolwork interactive and engaging.

But is the message really getting through and being acted upon? And can the basis of scientific knowledge in experimentation really be taught while children do less and less hands-on, lab-based experiments?

Like many UK academics, I have the impression over the last decade-plus that students starting university degrees in the biomedical sciences have done rather little practical work in the later years of secondary school. When I began interviewing prospective undergraduates – final year school pupils – 10 years ago, one of my standard questions was 'what was the most interesting experiment you have done at school this last year?' But I soon stopped asking this, because I only rarely got an answer. Indeed, many could not remember anything about the few experiments they had done. Strangely, at least to me, many of the same students expressed a desire to work in scientific research.

So there is a disconnect here. Research as students read about it in the newspapers or in, say, *New Scientist*, seems high-tech and space-age, carried out in gleaming labs by modern wizards pipetting microlitres of mysterious solutions from one tube to another, or operating million pound scanners. Students fail to connect this with the basics – following a protocol, optimizing a method, careful repetition, observation, formulating and testing a hypothesis – as they themselves may have experienced them in school laboratories. The less practical science they do, the more this is true.

This problem has, to some extent, been recognised. There have been reports by bodies such as CASE (formerly Save British Science) and NESTA, learned societies have voiced their concern, and government strategy documents repeatedly recognise the need for science teaching to be grounded in experimental work. Some of the pressures reducing the amount of practical science in secondary (high) schools – overworked teachers, ageing labs and equipment, overstuffed test-driven curricula, fears (often misguided) about health and safety – have been identified, though not solved.

However, I think more work is still needed at the grass roots from practising scientists – us – and critically at the institutional level in our departments, faculties and universities.

One goal should be to de-mystify research and the people who do it, by sending scientists out to schools to make the link between school science (and the grounding in experimental scientific method it should provide) and real research. There are schemes to do this, including the Researchers in Residence scheme for PhD students. But much more still needs to be done.

Another problem that I think needs addressing is the distance between professional scientists – the experts in experimentation and the principles upon which it is based – and decisions about exactly what practical science is done in school classrooms. One might expect that scientific professionals would have a close interest in the details of how experimental science is first introduced in the early school years, and how it is taught in the years through to university entry. But we have been guilty, as I see it, of not getting much involved beyond agreeing 'there should be more of it'.

Part of the reason, I suspect, is that the training of science teachers – the key people in helping pupils comprehend scientific method – is almost completely dominated by educationalists. In case there is any confusion, an educationalist is defined by most dictionaries as 'a specialist in the theory of education'. University scientists are scientific educators, often of considerable experience. In the main, though, they are not educationalists, and do not wish to be. Personally, I feel that professional scientists should be directly involved in the postgraduate training of secondary school science teachers. While most people would agree that a classroom science teacher needs an understanding of the theory of education, they also need a good grasp of practical science, its importance, and how to translate it to the classroom setting. At present, we assume in the UK that all the scientific background necessary to do this is acquired adequately during a B.Sc. degree course. I remain unconvinced about this, especially when the course in question quite possibly contains no lab-based work beyond the second year. Of course, it is true that teachers acquire much of their skill and knowledge through the process of having to explain things in the classroom, in much the same way that university physiologists traditionally learnt basic integrative physiology by demonstrating and explaining it in lab classes and tutorials. But there is surely a role for experienced university teachers in helping mentor trainee science teachers through some of this process, along with the current and ex-classroom teachers who presently undertake the job.

Next there is the question of what experiments schoolchildren can actually do. It is not clear to me how the 'bank' of experiments gets renewed, except that I see little evidence that working scientists are involved, which worries me. If we want to come up with new and interesting science experiments for schoolchildren, fit for the 21st century, my starting point would be design teams that should include professional scientists along with the experienced classroom teachers and the educationalists.

So action is needed at all levels. Individual, societal, and institutional. As individuals, there are many ways to get involved. I hope many of us will, and perhaps the suggestions above might offer some ways.

Learned societies can help, and are helping, both by lobbying, and by spreading information about how to get involved. Maggie Leggett, writing in *Physiology News* a year or two back about public communication and engagement, suggested that the key role of learned societies was likely to be as places where people could exchange information on what approaches they had tried, what worked, and what didn't. I am sure there are many members out there who have engaged in initiatives to help with science education. But I do not know who or where they are, or what they have done. Building up web-based registers, talk-boards, and resources to help with this information exchange seems a role tailor-made for learned societies, and the Physiological Society is increasingly active in this regard.

Underlying all this is the role of institutions, and here I mean, specifically, 'scientists' employers'. In particular, universities have to decide whether this is something they care enough about to pay academic staff to take an interest in it, given that this may take time away from other activities. I think it is time for UK universities to grasp this particular nettle. The first step, which many universities and faculties have now taken, is appointing specialist personnel tasked with things like schools liason, community outreach, and external affairs. But these people are primarily co-ordinators, and their success will rely critically on being able to recruit enough willing participants from inside universities. This will depend on institutional leadership, and on recognition of the importance of the job to the point where it is seen as a core part of at least some scientists' responsibilities.

We can all agree that ultimately, if enough children are not getting interested in science, there will be a gradual decline in the number of high-quality undergraduates, and subsequently of scientists. We need action now, particularly from universities, if this is to be tackled.

Austin Elliott

Physiology at UCL in 2006

The Physiological Society Main Meeting, 4–7 July

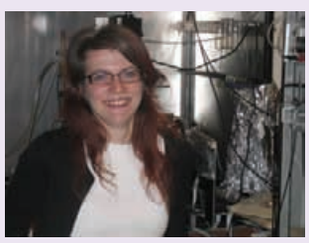
It is with great pleasure that the UCL Department of Physiology welcomes The Society back to London for its annual Main Meeting. The Department is currently busy with final preparations to ensure that your visit to London in July will be a veritable feast of science and social activities. This will be the second of The Physiological Society's new style Meetings and we hope that London will prove to be every bit as exciting as the first, held last year in Bristol.

So far everything is looking good. Exciting Plenary and Prize Lectures; not forgetting the second Physiological Society Public Lecture to be delivered by David Attwell, our own Jodrell Professor of Physiology. There will be a number of workshops including *Neuroscience methodologies*, *Teaching* and *Careers in science*, as well as 16 specialist symposia and a total of nearly 400 Abstracts to be presented over the three days of the Meeting. The Main Meeting will be preceded by the Young Physiologists' Symposium, *From molecules to behaviour* on 3–4 July. All this will provide something of interest for even the most refined of physiological tastes.

Research at UCL Physiology

UCL Physiology has a strong reputation in cellular neuroscience, cell signalling and systems physiology. Details of the research interests of individual groups can be found on our new web site (www.physiol.ucl.ac.uk). Our research is conducted by 30 academic staff, 11 senior research fellows, 40 post-doctoral scientists and around 30 PhD students. Research activity is flourishing. Members of the Department attract approximately £17 million in research grants from the main UK research councils and charities. An influx of JIF and SRIF funding has provided nearly £12 million pounds for improving the Department's infrastructure. This has facilitated the bringing together of research groups into modern well equipped laboratories. The UCL tradition of undertaking world class research in Victorian conditions is a claim we can no longer justify. Instead, we have new buildings, refurbished corridors, and more central facilities to encourage and support interdisciplinary research. Of course, there is plenty more to do, as some members of the Department will testify, but delegates will notice big changes since the last Society Meeting at UCL in 2001.

Our research falls into a number of defined areas. There is considerable and desirable overlap in some areas which facilitates collaboration. We aim to use a multi-disciplinary approach that combines



molecular and bioinformatics techniques with electrophysiology, whole animal recording and intracellular imaging using confocal and multi-photon microscopy. We have recently expanded in these areas through the recruitment of new staff and by investment in new *in vivo* and *in vitro* multi-photon facilities. Dedicated mechanical and electronics workshops provide custom-made equipment that greatly facilitates those particularly difficult experiments.

Cell Signalling Group investigates how cells process the many messages received from the external environment. Lipid signalling (Shamshad Cockcroft and Geraint Thomas), and calcium signalling (Steve Bolsover, Sandip Patel, Jonathan Gale, John Carroll) are two signalling pathways that we study in a range of physiological systems including, the immune system, hair cells and oocyte and embryo development. Michael Duchen leads a diverse multi-disciplinary group that works on the role of mitochondria in the pathophysiology of cell function.

Cellular and Molecular Neuroscience Group is the largest in the Department. Members of this group have interests in the regulation of ion channel function (Paolo Pedarzani), synaptic transmission (Jonathan Ashmore, David Attwell, Angus Silver, Frances Edwards), and information processing (Andy Batchelor, Michael Hausser). A JIF bid led by David Attwell and colleagues in Physiology and

Pharmacology provided funding for the Andrew Huxley Building, which was recently opened by Lord Sainsbury and Andrew Huxley, as well refurbished labs for five groups. The group has recently been strengthened by new appointments. Josef Kittler provides a much needed strength in molecular neuroscience and is interested in the molecular and cellular mechanisms regulating the trafficking of GABAA receptors. Troy Margrie and Tom Mrsic-Flogel (arriving in October) will use functional *in vivo* imaging including multiphoton microscopy to explore mechanisms of sensory processing.

Autonomic Neuroscience has been a long standing interest in the Department based at The Royal Free Hospital. Mike Gilbey, Dave Jordan and Mike Spyer lead groups in this area, focused mostly on the control of respiration. Alexander Gourine has recently been awarded a Wellcome Trust Senior Fellowship and we are well down the track with plans to move Alex and the Autonomic Group to the main campus over the summer.

The Epithelial Physiology Group of Ted Debnam, Robert Unwin, Brian King and Scott Wildman are also based at the Royal Free Hospital. Their work focuses on control of secretion in the kidney and the gut. This group is a joint venture with the Division of Medicine and will soon be strengthened with new joint appointments at professor and lecturer levels. This will provide a strong translational angle to the research that will span from molecular genetics of renal transport through to *in vivo* physiology.

Sensorimotor Control was the topic of a recent Physiological Society Focused Meeting at UCL. This Meeting was organised by Phil Harrison. Other members of the group include Linda Harrison, Margaret Mayston and John Stephens. The Group has strong ties with the UCL Institute of Neurology and with Simon Farmer. Interests include understanding the reflex pathways that control hand and shoulder movement in man and in patients with specific lesions in the pathway.

Clockwise from top left: Entrance to Physiology; Angus Silver and his new 'baby'; John Carroll, Tomoko Watanabe, Guilaume Halet and Tasos Siskoglou in the new cell physiology labs; Jenga Káradüttir in the Andrew Huxley Building.

Teaching physiology at UCL

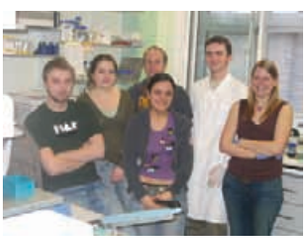
The Department teaches physiology to over 1,000 medical and science students. Everyone in the Department contributes to teaching either through delivery or organization of courses and modules. There are a core of individuals – Richard Tunwell, Linda Harrison, Jonathan Fry, Peter Tatham and Geraint Thomas – that run the teaching operation.

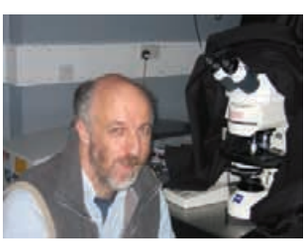
The ever-expanding student body has forced us to take radical steps in how we teach the large numbers of students in the first year. We are indebted to Chris Richards and the Department's new Teaching Fellow, Pamela Houston, for transforming our first year physiology course to include online tutorials and automatic assessment techniques. We remain committed to practical classes and students continue to learn the experimental nature of physiology in all 3 years. Many also opt to undertake a 9 week research project in their third year.

The social programme starts with a Wellcome (sic) Reception on 4 July. This will be an opportunity to explore the very impressive new home of the Wellcome Trust. The Society Dinner on 6 July steps away from the traditional and will take the form of a BBQ in our local green space, Regent's Park. Marquees, Pimms, spit-roasted beasts, a string quartet and perhaps even a fire-eater will make this one summer soirée not to be missed (barring, of course, meteorological interventions – in which case the marquees will prove snug and popular). In addition to these scheduled events the central London location of UCL will ensure that there are plenty of restaurants, pubs and clubs to cater for every physiologist's tastes.

John Carroll
Department of Physiology, University College London, UK

Prize Lectures at UCL (p. 15)





From the top: No worries, we can build it – Duncan Farquharson and Alan Hogben, Mechanical Workshop; all smiles – Matthew Duckett and Mark Todd in the Teaching Office; new boy, Jo Kittlerr, with members of his lab – Andrew, Alison, Marzieh, Jo, Chris and Kate; Raffaella Bosurgi, Raffaella Tonnini, Paola Pedarzani, Derek Costello and Ruth Taylor in the new neuroscience labs; Michael Duchen – getting to grips with the new multiphoton imaging system.

The original Physiology Laboratory at UCL was found in the North Wing of the main College Building, above the Slade School. In the stairwell there is a memorial plaque. Starling appointed as Jodrell Professor in 1899, was dissatisfied with the accommodation and set about having a large new department, which was completed in 1909 within a year and cost £20,000 to design, build and equip. Starling notes 'Ironwork outside staircase (Mr T Elsley)...£135'. There were novel architectural features and, over the front, one can see in gilt letters *Institute of Physiology* in art nouveau style. This was a tribute to the German fashion admired by Starling, and 'much disliked by the then Provost, who thought he scented secession' (Lovatt Evans,1964).

Tim Biscoe
Honorary Member

Lovatt Evans C (1964). *Reminiscences of Bayliss and Starling*. Cambridge, The University Press.

Physiology at UCL: past present and future

The Physiology Department at UCL has a long and distinguished history that has been entwined with The Society from the outset. From its origin in the 19th century, members of the Department (including Burdon-Sanderson, Sharpey, Sharpey-Schafer, Starling, Bayliss, Lovatt-Evans, AV Hill, GL Brown, A Huxley, B Katz and many others) have made major contributions to physiological science. Three of these physiologists, Hill, Huxley and Katz were awarded Nobel Prizes for their efforts. The role the Department played in fostering the discipline of physiology in the UK is illustrated by the fact that the first Meeting of The Physiological Society was held in Burdon Sanderson's house in College.

Today the majority of the Department exists in the original Institute of Physiology building. Built in 1909 under Starling's direction (see Tim Biscoe's piece below), the Institute subsumed the old UCL school playground, perhaps starting a fad that may go some way to explain why the UK may excel in physiology and not in events of a more sporting nature. Developments and mergers over the years have seen the Department expand and it now includes the three floors of the old medical school in the Rockefeller Building and laboratories at the Royal Free Hospital. More recently, members of the Department have taken a leading role in establishing the Ear Institute just east of the main campus. The Department currently consists of more than 100 members and research interests range from molecular cell physiology right through to *in vivo* studies concerning sensory and autonomic neuroscience, regulation of respiration and motor control (see p. 4 for more on our research interests).

For the future, physiology will remain a major discipline at UCL. However, the university structure in which we conduct our research may end up radically different from that which we currently enjoy. Physiologists in the UK and beyond will have endured university restructuring and reorganization, with departments in Cambridge and Oxford being the most recent. The passion for restructuring has now hit UCL and the long term existence of our traditional departments within a faculty of life sciences is under review. Super-faculties of biomedicine and health and disease-driven institutes are the order of the day. Perhaps it is time to accept the inevitable cycle of fashion and reinstate the 'Institute of Physiology', perhaps with a splash of 'integration', 'translation' and a good dose of medicine.

Joint International Meeting with the Brazilian Physiological Society

Ribeirão Preto, 319 km from São Paulo, will host the 41st Congress of the Brazilian Physiological Society from 27 to 30 August. It will be held jointly with The Physiological Society. Since both partners seek the advancement of physiology as an integrative science aiming at the understanding of the mechanisms that explain how the body works, a most exciting and productive encounter can be anticipated.

For the last 2 years the Organizing and Scientific Committees have been directing efforts to ensure that the Meeting will attract scientists – both faculty and students – dedicated to all areas of physiology. The programme has been carefully planned to allow the attendees to find up-to-date information as well as providing time to discuss and debate science with their peers. Congresses offer an excellent opportunity to meet one's professional friends, be introduced to others, and share different opinions and cultural perspectives.

The Convention Centre of Ribeirão Preto, venue of the Congress, provides the latest high technology facilities. It is located in the heart of the town, close to many hotels and commercial areas. The airport can be reached within 15 minutes from the city centre by car.

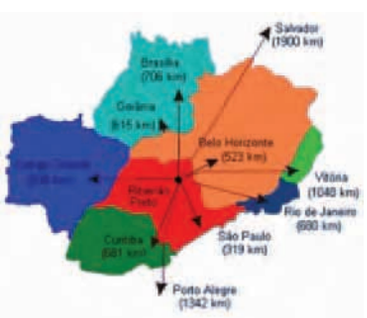
The Brazilian Physiological Society, as the local host, is looking forward to welcoming you to Ribeirão Preto in August and to chatting over a cup of good Brazilian coffee!

A history of the Brazilian Physiological Society

The Brazilian Physiological Society (SBFis) was established in 1957 by the initiative of some of our country's most eminent physiologists in an effort to promote physiology, encourage interchange of ideas and to improve the opportunity of young researchers to meet and discuss their projects and ideas with eminent physiologists.

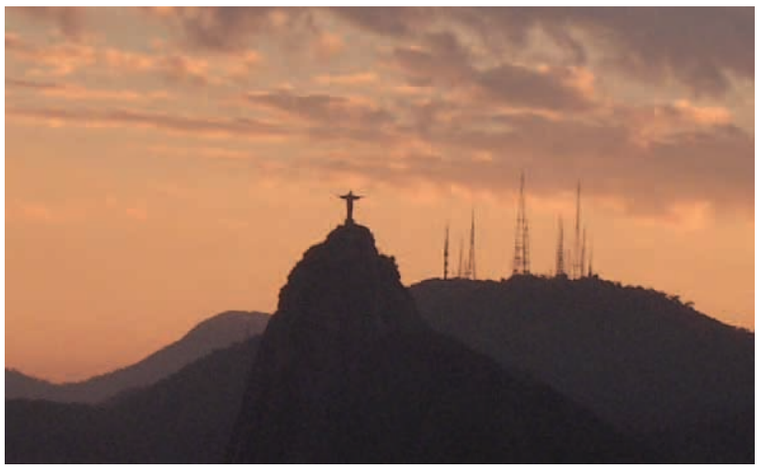
Since then, Congresses of the SBFis have been held every year and the President, Secretary and Treasurer elected every 3 years.

In the past 20 years the SBFis has established numerous scientific commissions in various specialised areas of physiology, such as undergraduate and graduate teaching and scientific committees. SBFis also



From the top (above): the Metropolitan Cathedral of São Sebastião in Ribeirão Preto, located at Praça das Bandeiras; Francisco Schmidt Coffee Museum in the botanical gardens of the Historical Museum; Buzios-Rio; map showing the location of Ribeirão Preto; current SBFis President Walter Zin.

Left: Petropolis, near Rio (top) and Bahia-Salvador.



Top: Christ the Redeemer, Rio de Janeiro;
Above: Sunset by the riverside in Belem do Para in the delta of the Amazon River.

organised a number of symposia and regional meetings, as well as advised the Scientific Program Committee of the Federation of Societies for Experimental Biology.

In 1956, 1961 and 2003 the SBFis organised joint meetings with the Latin American Association of Physiological Sciences, when it was given the opportunity to promote the interchange amongst eminent Latin American and other scientists from abroad, young graduate and undergraduate students, interchange of experiences, as well as the establishment of scientific cooperations among Brazilian physiologists. The last joint meeting of the ALACF with the SBFis – *Challenges for the advance of physiology in the third millennium* – was held in Ribeirão Preto, São Paulo, Brazil, and was attended by 1244 international scientists.

Current Officers of the Brazilian Physiological Society

Walter Araújo Zin (President)
Francisco Tadeu Rantin (President-elect)
Patrícia Rieken Macêdo Rocco (Secretary)
Denise de Carvalho (Treasurer)

The main goals of the SBFis

• to stimulate research leading to the progress, diffusion and knowledge of physiological sciences

• to stimulate the improvement of methods to teach physiological sciences according to modern technologies

• to promote remarkable training of physiologists in order to strengthen the physiological sciences in our country and abroad

• to encourage the young scientist to be involved with the understanding of systemic physiology, combined with new technological developments (molecular, genetics, immunology, imaging, etc.)

• to promote the integration between basic and applied research

• to support the participation of young scientists and students in the meetings

• to promote cooperative work between research groups.

José Antunes-Rodrigues
Brazilian Physiological Society

International Union of Physiological Sciences

I hope that Members of The Physiological Society will be particularly interested in the future of the IUPS, not least for the reason that The Society will be hosting its 2013 Congress. Members are encouraged to send their views on IUPS to the Long-range Planning Committee.

The article mentions the IUPS Africa Initiative. This was mentioned in a previous issue of *Physiology News* (**59**, 10) and several Members of The Physiological Society have kindly written to offer help. We are currently trying to organise plans with both African and IUPS colleagues.

Finally, links with the IUPS can only be further improved by the recent announcement that its Secretary General (Ole Petersen) will become the next President of our Society (see p. 44).

David Eisner
International Secretary

The following update on IUPS activities is adapted, with permission, from the first of a newly established series of IUPS Editorials in Physiology *(**21**, 2).*

The most important recent IUPS event was the 35th International Congress of Physiological Sciences held in San Diego, California, from 31 March to 5 April, 2005. This Congress had many new features, including a very successful series of tracks covering some of the most important current physiological themes. As part of Experimental Biology, there were ample opportunities to benefit from, and participate in, events organized by friendly neighbouring subjects and for

members of these other societies to see what physiologists had to offer. With more than 10,000 registered participants, this gave unprecedented exposure to physiological research at a time when this subject is undergoing a major revival.

The 35th IUPS Congress in San Diego provided a much needed replenishment of IUPS resources. We therefore have good reasons to be very grateful to the American Physiological Society (APS), not only for organizing a superb scientific event, but also for helping the IUPS rebuild our finances so that we may again plan major initiatives. As described in the 2004 and 2005 IUPS Newsletters (http://www.iups.org), the scientific programme for the San Diego Congress was generated by the IUPS International Scientific Program Committee (ISPC) in cooperation with the APS under the chairmanship of Walter Boron. Walter did a fantastic job for which IUPS is extremely grateful.

The San Diego Congress also represented the crowning achievement of IUPS President Allen Cowley, Jr. Allen was an outstanding President, responsible for a major restructuring and streamlining of the Union's Commission Structure, which did much to facilitate the scientific programming process for the San Diego Congress.
During the San Diego Congress, the IUPS Council (for composition see the IUPS web site mentioned above), chaired by Akimichi Kaneko, who at the General Assembly in San Diego was elected to succeed Allen Cowley as IUPS President, met several times and a number of important decisions were made. The following three are perhaps of particular significance:

• a Long-Range Planning Committee (LRPC) was established, under the chairmanship of Denis Noble, who served as IUPS Secretary General from 1993-2001, when Ole Petersen took over. Denis has since completed the composition of this key Committee. We are grateful to Denis, Allen Cowley, Cecilia Hidalgo, and Yasunobu Okada for taking on this task. The Committee will present its report, making recommendations on future IUPS activities, as well as their resource implications, to the IUPS Council when it meets again in 2007. The LRPC is now seeking opinions from member societies and/or individuals on the future of the physiological sciences, the organization of IUPS, IUPS meetings, finance, relations with the International Council for Science (ICSU), the United Nations Educational, Scientific and Cultural Organization (UNESCO), International Brain Research Organization (IBRO), and other international organizations, as well as on public relations.

We are very interested in receiving opinions from a wide range of the scientific community. Anyone wanting to comment on these issues should write to Denis Noble via the IUPS Secretariat in Paris (e-mail: orsoni@chups.jussieu.fr).

• Council also elected a committee to come forward with specific plans for an Africa Initiative. Tony McKnight is chair, with Ann Sefton and David Oyebola as members. The Committee is expected to develop a strategy to be presented to a funding agency to culminate in a major workshop in Africa in 4 years. Council has allocated seed money to get this potentially important initiative under way.

• after 4 years of working with the Commission Structure established by the 2001 Council elected in Christchurch, New Zealand, it was decided to make some adjustments. Based on the experience of planning for the San Diego Congress, it was felt desirable to have a new Commission on Molecular and Cellular Biology. The two Commissions that had previously dealt with various aspects of the neurosciences were merged into one consolidated Neurobiology Commission. The new Commission Chairs are listed on our web site.

Although it may seem early, planning for the 2009 IUPS International Congress of Physiological Sciences is already under way. The 36th International Congress of Physiological Sciences will be held in Kyoto, Japan, from 27 July to 1 August 2009.

The IUPS ISPC has already been established (see box, left) and the first meeting took place in Osaka, Japan, on 20–21 January. At this meeting the fundamental policy for the generation of the scientific programme was established and a start made on the selection of Plenary Lecturers. Some details about the Congress are already available at the IUPS web site.

The IUPS Executive Committee also met in January and we hope to give information about the decisions made at these two meetings in due course.

Akimichi Kaneko
President

Ole H Petersen
Secretary General
International Union of Physiological Sciences

IUPS 2009 International Scientific Programme Committee

Chair
Yoshihisa Kurachi (Japan)

Vice Chair
Ole H Petersen (UK)

***Ex officio* members**
Akimichi Kaneko (Japan)
Pierre Magistretti (Switzerland)

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Hans Hoppeler (Switzerland)
Peter Hunter (New Zealand)
Caroline McMillen (Australia)
Ole Petersen (UK)
Quentin Pittman (Canada)
Irene Schulz (Germany)
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Curt Sigmund (USA)

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Associate Members
Yukiko Gotoh, Tadashi Isa, Fumihiko Kajiya, Yoshikatsu Kanai, Kazuyuki Kanosue, Itsuo Kodama, Masato Konishi, Osamu Matsuo, Katsuhiko Mikoshiba, Hiroshi Nose, Masahiro Sokabe, Miyako Takaki, Jun Tanji, Gozoh Tsujimoto, Tadashi Tsumoto, Toshihiko Yada, Megumi Yoshimura

My 10 key papers

The memorable papers that Alison Brading (right) still vividly remembers first reading

For my top 10 papers I have decided to include those that I still remember first reading, and which for me were memorable, so much so that for most of them, I can actually recall where I was when I read them. Most of the early ones came from *The Journal of Physiology*, because I was a Member of The Society early on (and later on the Editorial Board) and had time then to read anything in it that interested me. Only a few of these papers bears directly on my own research, but I am sure they influenced me indirectly, and all gave me considerable pleasure. I realise now how lucky I have been in my life as a scientist, because I eventually met virtually all of the authors, with the exception of David Marr. Looking at the selection I can see that, although I started academic life as a zoologist, and came to think of myself as primarily a physiologist, the fact that I have worked entirely in a pharmacology department has clearly had a significant impact! I will refer to the papers in their approximate date order.

1 Hodgkin AL & Huxley AF (1952). A quantitative description of membrane current and its application to conduction and excitation in nerve. *J Physiol* 117, 500-544

This paper I came across as an undergraduate. I was fortunate to do my first two degrees in what was then (I started in 1959), probably the best zoology department in the country. Going to Bristol University was largely serendipitous, because having missed 2 years after leaving school (through contracting polio) I was loath to waste another year getting my A- level work up to university entrance examination standard, which eliminated London, Oxford and Cambridge from consideration. Reading turned me down, but Bristol didn't seem to mind me being in a wheelchair, even though the layout of the department was totally unsuited to the disabled (for the first 6 months I had to drive 2 miles to find a lavatory I could use!). Under the chairmanship of John Harris, the course was a good traditional romp through the animal kingdom, but with an unusually large component of physiology. We were introduced to the Hodgkin and Huxley model of the action potential in the squid giant axon. I enjoyed a superficial acquaintance with the papers then, but later in my capacity as tutor for physiology at Lady Margaret Hall, Oxford, I read the papers more carefully, and began to really appreciate how beautifully simple and wonderfully predictive the Hodgkin Huxley model was. Hence my inclusion of this outstanding paper in my top 10 papers. It still pleases me, and I love pointing out to my students how each reproduction of the action potential required iterative solving of numerous different equations for every point, at a time when there were no computers and no calculators – a mammoth task!

2 Bülbring E (1954). Membrane potentials of smooth muscle fibres of the taenia coli of the guinea-pig. *J Physiol* 125, 302-315

This paper was of great importance to my future. During my PhD (a microelectrode study of the body wall musculature of the pig round worm, *Ascaris lumbricoides*) under the supervision of Peter Caldwell (who used to join the other physiologists who worked on squid axons in the Plymouth Marine Biological Centre at Plymouth in the summers), I was recording spontaneous electrical activity of a sort I had never seen in the literature, until I came across papers by Edith Bülbring's group. I saw to my amazement recordings of potentials very similar to mine (see Fig. 1).

As so little was then written about nematode muscle, I followed the smooth muscle literature, which in this country nearly all emanated in Oxford from Bülbring's laboratory. The paper I have included is one I read later, and only with hindsight did I realize what an amazing achievement this work was. Microelectrodes had not long been invented, and to record simultaneously membrane potential and contractile activity from strips of smooth muscle composed of cells only a few microns wide and moving spontaneously, was a stupendous achievement, not even

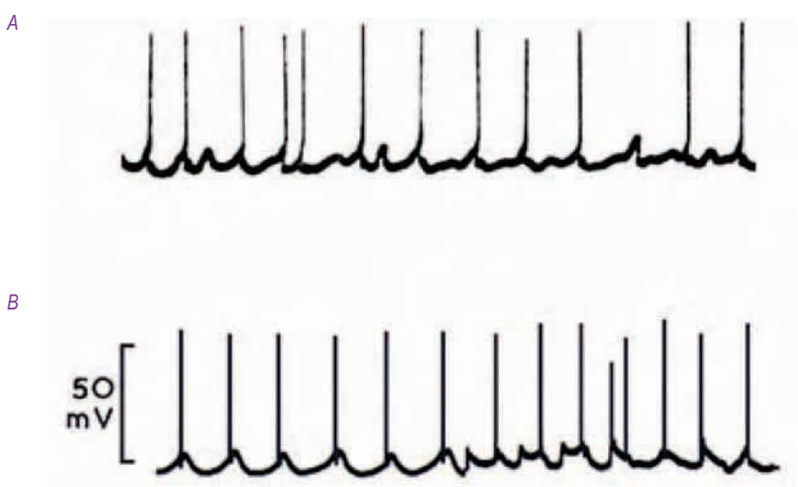

Figure 1. Comparison between action potentials in a nematode and a mammalian smooth muscle.
A, Ascaris lumbricoides body wall muscle (Brading thesis, 1965).
B, Guinea-pig taenia caeci (Bülbring, 1955).

matched that often in later work on smooth muscles. I became deeply interested in the smooth muscle work, and gratefully took up the opportunity to join Bülbring's group as a postdoc, hence sealing my future, and gaining in her a beloved mentor.

3 Tomita T (1966). Electrical responses of smooth muscle to external stimulation in hypertonic solution. *J Physiol* 183, 450-468

When I first joined Bülbring's laboratory Tadao Tomita was working with her. This ground-breaking paper, published soon after I arrived, had an enormous influence on research into the properties of smooth muscle. Using a long strip dissected carefully from the guinea-pig vas deferens, and a partition stimulating method to apply a uniform change in potential to the cells at the partition, Tomita measured the spread of the membrane potential change with distance from the partition using microelectrodes, and showed the then extremely surprising result that cable theory predicted the results, enabling the time and space constants of the tissue to be derived. For those interested, a detailed theoretical model is described in Tomita, 1966 and shows how the membrane resistance and capacitance could be measured. The implication of the paper was that the smooth muscle cells in the vas deferens were composed into functional bundles in which the cells were electrically interconnected in three dimensions (see Fig. 2). Tomita became one of my heroes. An enormously intelligent scientist with a background in physical sciences, and a superb experimentalist, he was nevertheless a modest man, and hated confrontation. It was difficult to persuade him to interpret his results in his papers, because he believed that if he just gave his results everyone else would be intelligent enough to see the implications. At that time another active group of smooth muscle researchers were attempting erroneously to measure membrane properties in smooth muscle tissues by injecting current into single cells through a microelectrode, which Tomita's work had clearly shown to give grossly inaccurate results.

Because this group were influential, we tried to persuade Tomita to discuss their work with them, but he would not. However, at an International meeting in Munich their group were seated at a table close to ours at the main dinner. On the table also were quite large shots of schnapps for each delegate, and the beer flowed freely in litre steins throughout the meal. Playing on the common difficulty in metabolizing alcohol that many Japanese have, we waited until Tomita's inhibitions were sufficiently blunted, and pointed him in their direction. I am delighted to say that he was able to convince them of their basic error, and to do it in a manner that kept a friendly relationship between the groups.

4 Marr D (1969). A theory of cerebellar cortex. *J Physiol* 202, 437-470

The next paper on my list has nothing to do with smooth muscle, but hit my attention when reading the then current issue of *The Journal*. I remember coming across it in the departmental library and staying there to read it through, which took me several hours! This was a real 'eye opener' and extremely exciting. It was the result of Marr's work during the tenure of a research studentship at Trinity College Cambridge. Based largely on the detailed anatomical findings of Eccles, Marr put forward a remarkably complete theory of how the cerebellum could learn to perform motor skills, and made some predictions. The most important prediction was that 'the synapses from parallel fibres to Purkinje cells are facilitated by the conjunction of presynaptic and climbing fibre (or post synaptic) activity' in other words behaved as suggested earlier by Hebb (1949). In spite of the fact that evidence now suggests that the conjunction of activity actually depresses rather than facilitates response to parallel fibre input, this paper for the first time gave the feeling

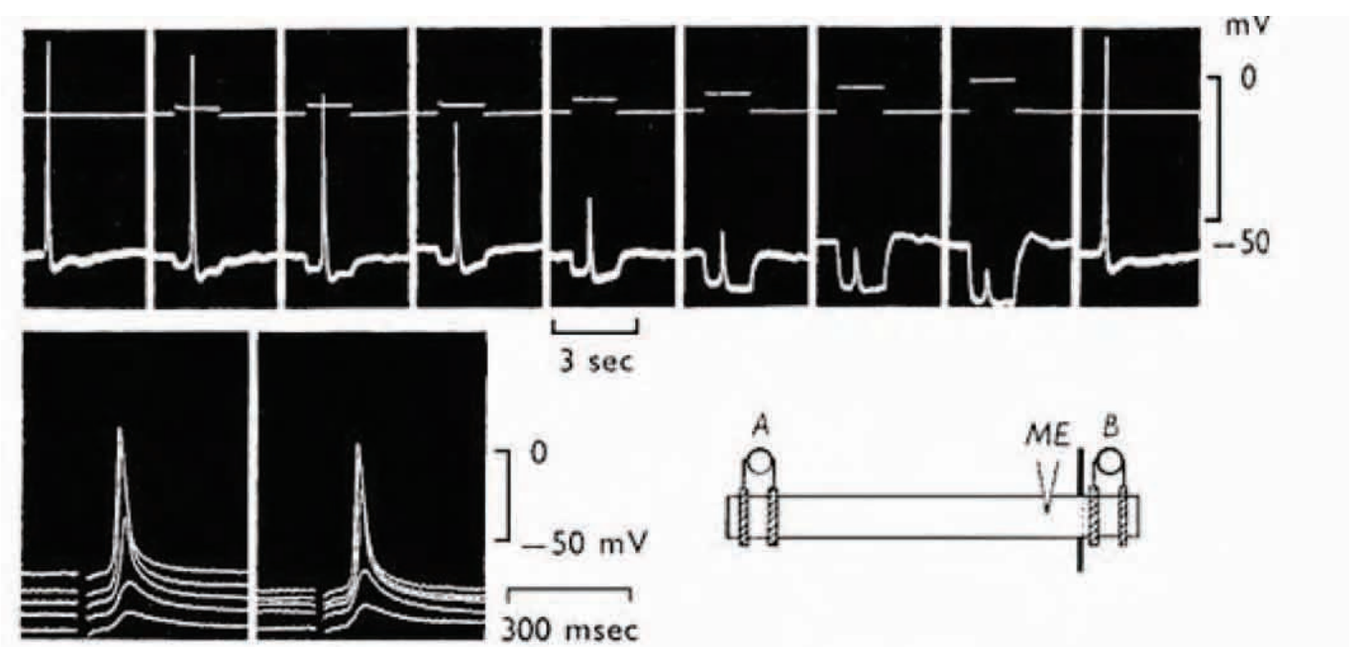

Figure 2. The effect of hyperpolarization on the action potential of guinea-pig vas deferens. Conditioning stimuli were applied at *B*, the membrane potential was measured with a microelectrode (NE) near the partition, and action potentials were evoked by the electrodes at *A*. From Tomita, 1966.

that it might be possible to understand neural processing. The thinking of this remarkable scientist and mathematician continues to have a major influence in understanding of CNS processing in spite of his tragically short career (he died of acute leukaemia in Cambridge, Massachusetts at the age of 35).

5 Katz B & Miledi R (1972). The statistical nature of the acetylcholine potential and its molecular components. *J Physiol* 224, 665-699

I had long been a fan of Katz and Miledi and read most of the earlier papers on the neuromuscular junction. This one published in *The Journal* took a huge step forward. For me it was particularly exciting, because it threw light on the behaviour of the nicotinic receptors, and I had become interested in receptors (through coffee time discussions with Humphrey Rang and Jim Ritter). This unusually long (for them) and detailed paper arose from the observation that bath applied acetylcholine generated not just depolarization, but an increase in the noise of the recording. In a lecture he gave to The Physiological Society after his retirement, Katz told how they had to change their tissue bath in order to administer exogenous acetylcholine (previously they had just studied nerve evoked responses). With the new bath, they initially thought that that the noise that always occurred when they opened the tap to allow the drug access, was spurious, and they spent many hours trying to find the external source, before eventually realizing it was in fact a genuine phenomenon, and would be expected to give information about the underlying molecular events. They chose to analyse the noise (initially by projecting traces onto the screen of the UCL physiology lecture theatre and measuring things with a ruler!) with the assumption that it was caused by random occurrence of 'shot' events caused by opening of the channels for a particular duration, and estimated this from their analysis as being of 1 ms. The two state model they proposed, namely:

$$A + R \Leftrightarrow AR \Leftrightarrow AR'$$

with two forward and two backward rate constants is now a commonly used two state model for directly coupled receptors, with a binding event and an isomerization. Interestingly, however, as pointed out by Andersen and Stevens (1973) in *The Journal* later the same year this model predicts the channel open duration would vary about a mean, rather than being a 'shot' event, and using this assumption these authors calculated a mean channel open time some five to six times longer. After his retirement, Katz was an Editor of *The Journal* during my tenure as a Distributing Editor, and was a godsend. He dealt with his mail in order each day, and when he came across a paper to review, did it immediately and sent it back by return of post!

6 Ascher P, Large WA & Rang HP (1979). Studies on the mechanism of action of acetylcholine antagonists on rat parasympathetic ganglion cells. *J Physiol* 295, 139-170

This is another paper I came across in *The Journal*. Rang had left the department by then for a transient period at St George's, but I followed his research, and this paper struck me as a good one. Taking advantage of the simple morphology of ganglion cells, the authors were able to use a two microelectrode voltage clamp technique to measure currents through nicotinic receptors activated by various agonists, at a range of different holding potentials, and then to examine the effects of antagonists. I very much liked the approach taken in the paper, and the use of various techniques such as voltage jump etc. to build up a convincing picture of how the antagonists were working. In particular it showed clearly the difference between the drugs that blocked through classical competitive antagonism and those that were non-competitive. It provided excellent evidence that these non-competitive drugs were acting as channel blockers. As far as I am aware this is the first and only time anyone has clearly demonstrated how a non-competitive receptor antagonist is working. Interestingly tubocurare, which at the neuromuscular junction does act as a competitive antagonist, at ganglia acts predominantly as a channel blocker, as does hexamethonium, which has little effect at the neuromuscular junction. This highlights the differences between nicotinic receptors at the two sites, and sheds further light on the channel properties.

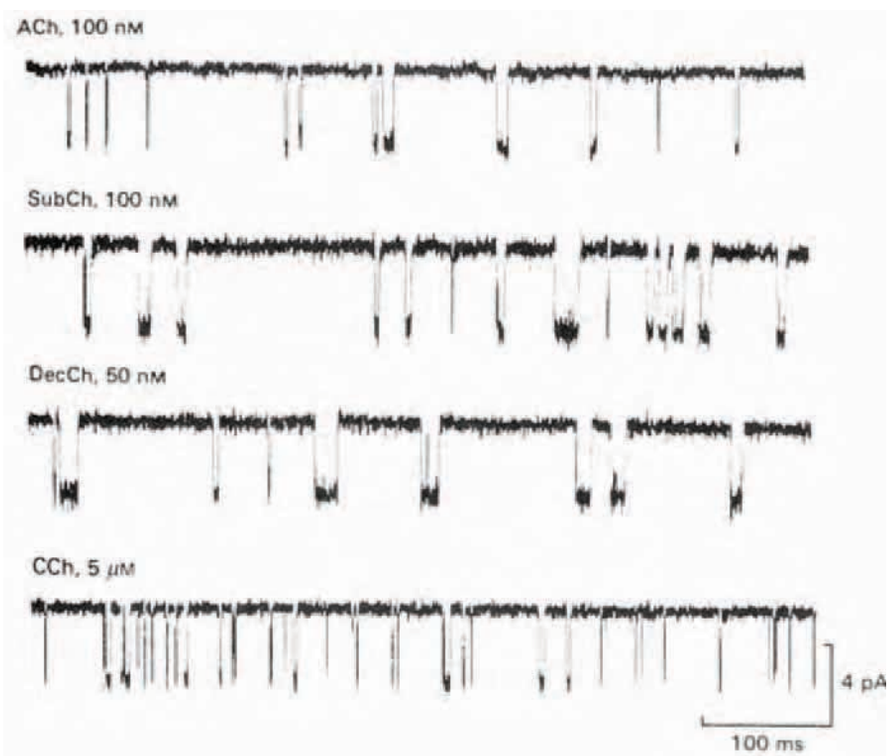

Figure 3. Patch clamp recording of single nicotinic acetylcholine channel activated by four different agonist drugs. Adapted from Colquhoun & Sakmann, 1985.

The last four papers were not published in *The Journal*, but came to my attention in other ways. Continuing with the theme of channels and receptors, for a period indirect methods such as noise analysis and voltage jumps became the methods of choice for studying channel properties, until, that is, the coming of the patch clamp.

7 Neher E & Sakmann B (1976). Single-channel currents recorded from membrane of denervated frog muscle fibres. *Nature* 260, 799-802

Few people interested in channels can have missed this paper and will remember the great excitement the possibility of recording currents through individual channels generated. I am going to cheat here and include Hamill et al. (1981), the paper in which the improved giga seal method was described. This method allowed visualization of the opening and closing of individual channels in a wholly satisfying way, giving definitive proof of the underlying theory of the agonist generated noise. I am constantly amazed and delighted that we physiologists can follow the behaviour of single molecules in real time, with comparatively simple and cheap apparatus whilst the biochemists with their enormously expensive technology are still looking at populations! (see Fig. 3)

8 Brock JA & Cunnane TC (1987). Relationship between the nerve action potential and transmitter release from sympathetic postganglionic nerve terminals. *Nature* 326, 605-607

This paper describes another breakthrough arising from application of a simple experimental approach, that of recording activity from underlying nerves and smooth muscle cells in the vas deferens using an extracellular glass electrode – a sort of loose patch. This approach brought about a huge increase in our understanding of autonomic neuromuscular transmission, particularly from sympathetic adrenergic nerves, and began to revolutionize thinking. The general view that autonomic nerves released transmitters that diffused towards the underlying smooth muscles, and bathed them in transmitters (a view based on the ease with which smooth muscle respond to bath applied agonists, the lack of specialized endplates and the apparent rarity of nerves in EM sections of many smooth muscles), had to be revised, since it was now possible to record the invading action potentials at the same time as any subsequent currents resulting from transmitter release on the smooth muscle. What these authors clearly showed was that in the varicose nerve terminals release of a quantum of transmitter from a release site was a rare event (as low as only 1 release for 100 action potentials when the frequency of stimulation was low) and caused a discrete transient response of the innervated cell. The intermittency was not caused by failure of the action potential to invade the terminals. It was now possible to compare quantal release from autonomic nerves, with that at the NMJ, and also with individual synapses in the CNS, (being studied at that time in Oxford by Julian Jack's group). The ability to study release from single release sites has of course allowed huge advances in understanding of how synaptic release is modulated, and links up with the Marr paper and the expanding fields of study into long-term depression and facilitation in the CNS.

9 Colquhoun D (1998). Binding, gating, affinity and efficacy: the interpretation of structure-activity relationships and of the effects of mutating receptors. *Br J Pharmacol* 125, 924-947

Maybe I am now a pharmacologist! This paper impressed me enormously, and addresses a fundamentally pharmacological problem, addressing the issue of whether or not it is possible to measure efficacy (the ability of an agonist to activate a receptor) and affinity (the ability of the agonist to bind to the receptor) as separate entities. Probably not. I have been fortunate in knowing this eccentric brilliant pharmacologist, and am grateful for his patience for the many times when I ring him up asking him to explain some point or other abut receptors. This is a long paper, but full of insight and wisdom.

10 Gabella G (1995). The structural relations between nerve fibres and muscle cells in the urinary bladder of the rat. *J Neurocytol* 24, 159-187

This last paper is relevant to the research area in which I have spent most of my time in recent years, that of the control of the urinary bladder. I met Giorgio through Edith Bülbring, and he has also become one of my heroes. He is clearly a brilliant microscopist, but his work stands out because it is always designed to illuminate some key physiological or functional point. I have spent many happy hours pouring over his electronmicrographs gaining insights into the tissues and their functions. In this paper, to study in detail the relationship between the nerves and smooth muscle he cut serial sections for electron microscopy to reconstruct the varicosities. This is a technical tour de force, and the time, effort and patience to do this work is something few possess. Single sections do not allow the real density of the innervation to be appreciated, but this detailed analysis shows that each smooth muscle cell receives at least one close contact with a naked varicosity. The images are superb, and the results consistent with the growing belief that in many cases the autonomic nervous system does indeed make close contact with its effectors.

The fact that my top ten papers end in 1998, does not mean that I have not read more recent memorable papers, but that none of them have been memorable enough for me to remember where I was when I first read them, or maybe this is just a reflection of lack of available memory space in my ageing brain!

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My own subject

Hugh de Wardener recalls the trials and tribulations of self-experimentation in the 1950s

In the 1950s I worked in Professor Peter Sharpey Schafer's Department of Medicine at St Thomas' Hospital, and was one of the experimental subjects in three experiments on renal function.

In the first of these, we were measuring the effect of a vasovagal faint on renal blood flow (de Wardener & McSwiney, 1951) (Fig. 1). Fainting was induced by 'pooling' blood in the legs followed by a venesection from an arm vein. I was the first subject and the only one in whom pooling of blood in the legs was accomplished by sitting on a saddle on a tilting table set at 45 deg. with my legs unsupported. A steady flow of urine was ensured by intravenous mannitol. Urine was collected via a urinary catheter into small conical flasks firmly kept in place manually by the ward sister who had volunteered to help. As the venesection proceeded I suddenly lost my sight. I heard myself say 'I can't see anything' and then 'I feel sick' and I passed out. As I did so I am told that I vomited onto the back and head of the ward sister who grimly stuck to her task. The results showed that during the low arterial phase of the faint there was evidence of renal vasodilatation with little change in renal blood flow. Subsequently, we kept the subjects horizontal and pooled the blood in the legs with thigh cuffs, which proved more experimentally tractable.

In the second experiment we studied the effect of solute secretion on the production of a hypotonic urine in man (de Wardener & del Greco, 1955). The point in contention was whether the tubular fluid delivered to the distal concentration site was isosmolar or hypoosmolar. It was well kown that the induction of an osmotic diuresis resulted in a hypertonic urine which asymptotonically approached isosmocity. But to induce an acute osmotic diuresis it is necessary to give an intravenous infusion of hypertonic fluid. This stimulates anti diuretic hormone secretion thus raising the level of plasma ADH, which influences the distal concentration site thus obscuring the nature of the osmolality of the fluid that flows into it.

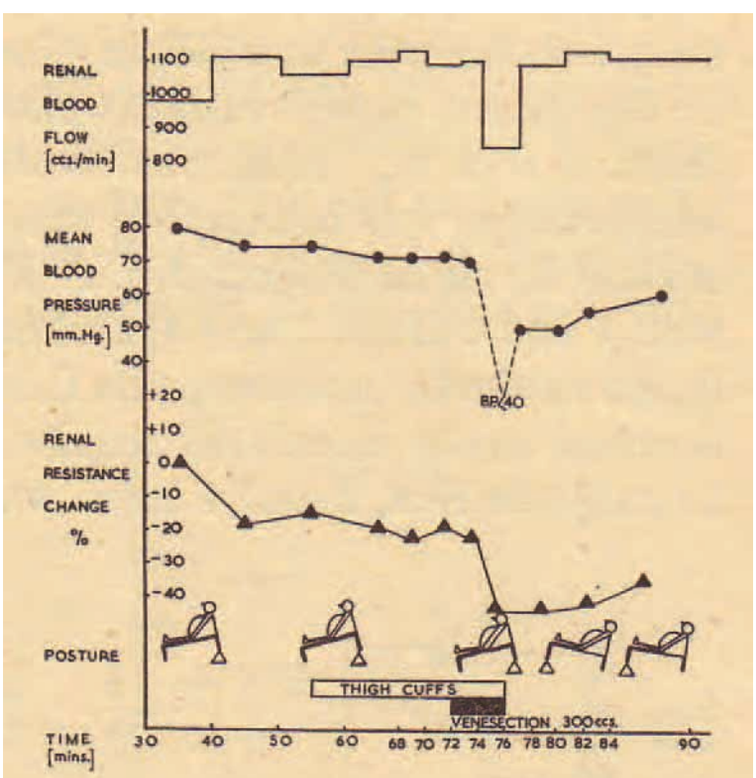


Figure 1. The effect of vasovagal faint on renal blood flow, showing the fall in renal resistance which occurred with the onset of hypotension (from de Wardener & McSwiney, 1951).

Hugh de Wardener (right) pictured with Adetokunbo Lucas at the Imperial College Faculty of Medicine annual award of fellowships ceremony in 2004.

I decided to explore the effect of an osmotic diuresis in the absence of endogenous vasopressin. As a preliminary experiment I decided to see the effect on my urine osmolality of inducing an osmotic diuresis, after having inhibited my hypophysis from secreting ADH with one large oral intake of alcohol. Once again I had a urinary catheter in place and two intravenous lines. As we were short-staffed at the time, I was also writing up the notes of the experiment as it went along. After several control periods, I drank 100 ml of 100% ethyl alcohol in about 1 minute. I came across the notes of this experiment a few years ago and, to my surprise, found that after drinking the alcohol the notes are written with a red biro. After some minutes there is a note 'I feel like singing' and a few minutes later 'Am singing'. The mannitol infusion was then given and the osmotic diuresis induced. Within a short time the combination of alcohol and mannitol gave me a terrible headache. But the results were encouraging and we eventually explored the problem in patients with diabetes insipidus in whom it was unnecessary to give alcohol.

The results were consistent with Shannon's hypothesis that the fluid entering the concentration site in the kidney is always hypotonic. One of the best demonstrations in favour of this hypothesis is illustrated in Fig. 2. The hypotonicity of the urine of a patient with diabetes insipidus was gradually reduced by a continuous infusion of

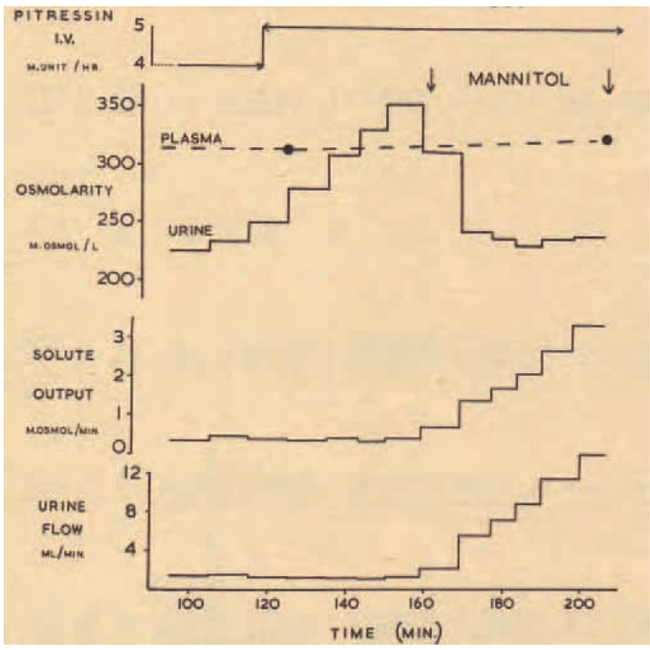


Figure 2. Effect of intravenous pitressin and concentrated mannitol on the urine osmolarity, solute output and urine flow. The urine osmolarity changed from hyper- to hypotonic upon the administration of mannitol (from De Wardener & Del Greco, 1955).

pitressin until it became mildly hypertonic. At this point, as the pitressin infusion continued, an osmotic diuresis was induced by intravenous mannitol, and the hypertonic urine duly became hypotonic.

The third experiment in which I was a subject was the most arduous (de Wardener & Herxheimer, 1957a; de Wardener & Herxheimer, 1957b). In the 1950s, when it was not possible to measure vasopressin, it was often difficult to distinguish diabetes insipidus from compulsive water drinking (psychogenic polydipsia). A period of dehydration was supposed to separate the two since the concentration of the urine of the compulsive water drinker, who has an intact hypophysis, should then resemble that of a normal person, i.e. it should be substantially higher than that from a patient with diabetes insipidus. I was impressed, however, by the relatively poor ability of patients with compulsive water drinking to concentrate their urine after a period of dehydration, and I wondered if this might be due to a functional adaptation of the kidney to the excess water intake. In order to determine whether this was true, it was necessary to measure the kidney's ability to concentrate the urine before and after a relatively prolonged period of overhydration.

Not surprisingly, I had difficulty finding volunteers until Andrew Herxheimer's curiousity about the effect of overhydration on saliva induced him to join me. We decided to drink 10 l of water per day for 10 days. The effect on the kidneys' ability to concentrate the urine was clear cut (Fig. 3). After 10 days the ability to concentrate had fallen from about 1,000 m.osmol/kg to approximately 500 m.osmol/kg. Many years later this phenomenon was shown to be due to a diminution in the number of aquaporins mobilised to the surface of the collecting tubule cells (Knepper, 1998).

Drinking that much water was most unpleasant. The tediousness and repetitiveness of overcoming one's increasing distaste for water was exhausting. It is very difficult to drink large amounts of water, day after day, when one is not thirsty. The large volume can only be managed by spreading the intake throughout the 24 hrs, so alarm clocks are needed at night. The most striking subjective feature was a feeling of coldness associated with pallor which varied in intensity. Emotional lability was pronounced, with bouts of hilarity alternating with moroseness. Appetite, however, was excellent throughout, though the food was tasteless unless one added large amounts of salt, and the very thought of adding salt caused profuse salivation. This was associated with a sharp fall in salt taste threshold which gradually returned to critical levels by the end of the period of high water intake.

After a week, to relieve the tedium, Andrew and I went over Lambeth Bridge to the Tate Gallery. The floor at the back of the Morris Minor was filled with numerous large glass containers, some empty for urine collection and others containing drinking water.

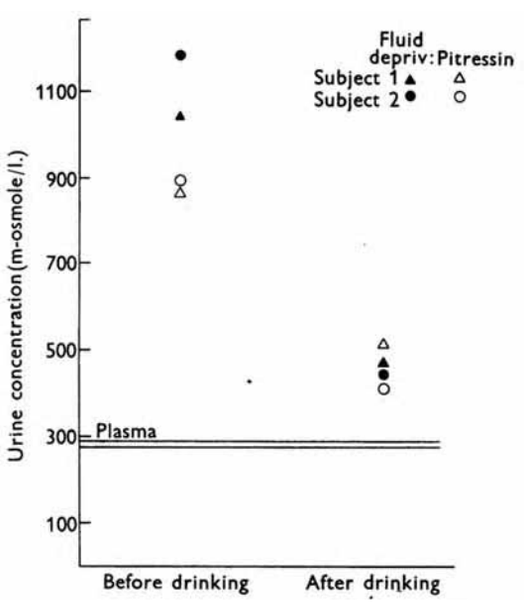
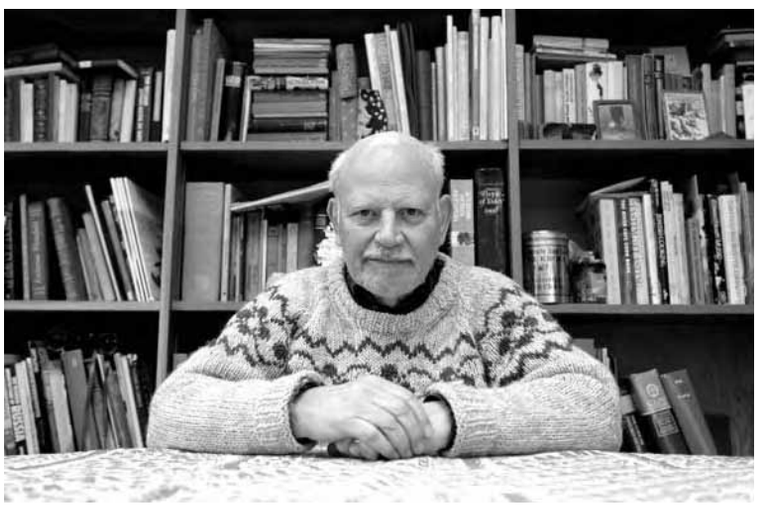


Figure 3. Urine concentrations following the intravenous administration of pitressin, and after a 26 hr period of fluid deprivation, before, and at the end of, drinking about 10 l of water a day for 11 days. The plasma osmolarity varied between the limits indicated by the two lines (from de Wardener & Herxheimer (1957a)



Hugh de Wardener (1960) (top left); Peter Sharpey-Shafer (top right) and Andrew Herxheimer (above)

Stupidly we had only labelled the sides of the containers, and not the tops, so that they were difficult to identify. One at a time we would come out of the museum, sit in the back of the car, drape a rug over our knees and empty our bladders into a container, drink some water and re-enter the museum. It wasn't long, however, before we began to have difficulty distinguishing the containers that held the drinking water from those that contained clear hypotonic urine, and we had to go back to the lab.

One at a time Andrew and I would sit in the back of the car, empty our bladders, drink some water and re-enter the museum

At the end, to test the kidneys' ability to concentrate the urine, we didn't drink anything for 24 hr. This last period seemed endless – we were disgruntled, unreasonable and cantankerous. The results, however, cheered us up no end.

Hugh de Wardener
Emeritus Professor of Medicine, Charing Cross Hospital, London and Fellow of the Faculty of Medicine, Imperial College, London, UK

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Prize Lectures

The following Prize and Plenary Lectures have been scheduled to take place at the Main Meeting of The Physiological Society at UCL from 4–7 July.

The Physiological Society Public Lecture – David Attwell (UCL)
The energetic brain
Tuesday, 4 July at 1830

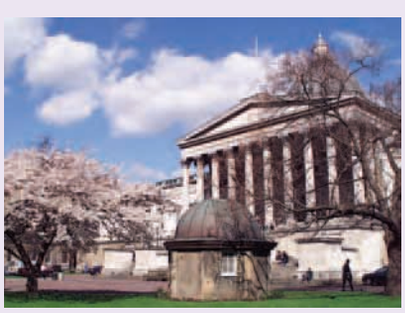
Biller Prize Lecture – Matthew Bailey (University of Edinburgh)
Mechanisms of hypertension in a mouse model of apparent mineralocorticoid excess
Wednesday, 5 July at 1200

Sharpey-Schafer Lecture – Neville H McClenaghan (University of Ulster)
Physiological regulation of the pancreatic beta-cell: functional insights for understanding and therapy of diabetes
Wednesday, 5 July at 1400

Hodgkin-Huxley-Katz Prize Lecture – Thomas J Jentsch (Universität Hamburg)
Roles of vesicular CLC chloride transport insights from disease, mouse models and biophysics
Wednesday, 5 July at 1815

Joan Mott Prize Lecture – Susan Wray (University of Liverpool)
Insights into the uterus
Thursday, 6 July at 1400

Wellcome Prize Lecture – Helen Kennedy (University of Bristol)
Detecting sounds: mechano-electrical transduction in the mammalian cochlea
Friday, 7 July at 1400



Targeted cell-based delivery of siRNA

Small interfering RNA (siRNA) is an ever more popular tool for silencing gene expression. But do experimenters always have to deliver siRNA directly into all the cells? Or can siRNAs pass from one cell to another via gap junctions? Ira Cohen and friends suggest that it all depends what connexins are around

The only direct form of intercellular communication in an ensemble of animal cells is provided by gap junction channels. All other forms of cell-to-cell communication must utilize the extracellular space. In vertebrates there are two unrelated families of proteins, connexins and pannexins, that form gap junction channels (Herve *et al*. 2005). In invertebrates another family of unrelated proteins, the innexins, serves the same function. Plant cells also communicate with each other; the structure they employ is called the plasmodesmata. Its pore diameter and length are both two orders of magnitude larger than that of any vertebrate gap junction channel and are known to allow passage of large solutes including siRNAs (Derrick *et al*. 1992; Staehelin, 1997; Vionnet, 2005).

In addition to passing ions to allow current flow, gap junction channels composed of connexins are permeable to a variety of larger molecules including nucleotides such as cAMP (Goldberg *et al*. 2004;Tsien & Wiengart, 1976). Although, Kolodny (1971) claimed that mRNA was permeable to gap junction channels his observations were compromised by a lack of controls for the actions of RNases. Hence, it was impossible to determine whether the molecules that moved from cell to cell were single nucleotides, multimers or combinations of both.

Because of the increasing therapeutic importance of siRNA, we decided to reinvestigate the permeability of gap junctions to short strands of nucleotides. We began by constructing tagged strands of nucleotides (morpholinos) of defined length and width. These oligonucleotides were resistant to the cells' nucleases (Mudziak *et al*. 1996).

To determine experimentally if gap junctions are permeable to morpholinos we delivered a known concentration through a patch pipette to one cell of a pair in which junctional conductance and fluorescence intensity of the tagged oligonucleotide are simultaneously monitored over time (Valiunas *et al*. 2005). Figure 1*A* illustrates the transfer of a morpholino oligonucleotide 12 bases in length between two adult mesenchymal stem cells. Figure 1*B* depicts how a morpholino might gain access to a gap junction channel. We found that synthetic nucleotides like those depicted in Fig. 1 up to 24 bases in length traversed gap junction channels composed of connexin 43, but not those composed of connexins 32 and 26.

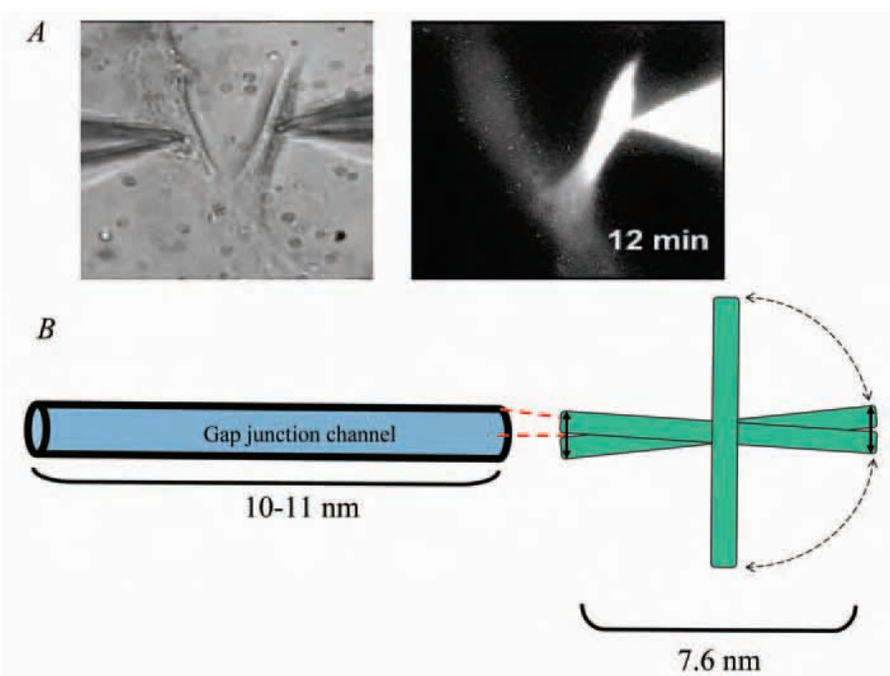


Figure 1. *A*, The stem cell to stem cell gap junctional permeability to a 12 base morpholino is shown. *B*, Any rod shaped oligonucleotide would be free the rotate about its axis in the cytoplasm as indicated by the dashed curved lines. The illustration depicts a 24 base morpholino with dimensions of 1.1 nm by 7.6 nm. To enter the gap junction channel a lesser angle of rotation (solid double arrows) is required. This illustrates that on the basis of the molecular rotation of a rod shaped species there is a finite probability of entrance into the channel.

These studies with morpholino oligonucleotides demonstrate that the transfer of siRNA from cell to cell via gap junctions might be possible. They also suggest that the permeability could be connexin-specific. To test whether siRNA itself could cross gap junctions, we needed to identify an siRNA known to silence a specific gene. We chose one directed against polymerase β, a gene involved in DNA repair (Polosina *et al*. 2004). To investigate possible cell-to-cell transfer of the siRNA, three cell populations were transfected with a cDNA encoding polymerase β siRNA. Cell type 1 expressed connexin 43, cell type 2 expressed connexins 32 and 26, while cell type 3 was communication deficient (expressing no connexins). For each cell type we co-cultured wild-type cells not expressing siRNA with cells transfected to express the siRNA against polymerase β. The experimental protocol then called for separation of the two cell populations to determine if siRNA transfer resulted in a reduction of polymerase β message in the wild-type cells. We found that cells expressing connexin 43 were unique in transferring the siRNA from the transfected to the wild-type cells, resulting in knockdown of polymerase β message. These results confirmed what our studies with the synthetic oligonucleotides had already suggested:

that gap junction channels composed of connexin 43 are sufficiently permeable to siRNA to facilitate silencing of a gene in an adjoining wild-type cell. The siRNA in this case was 22 bases long with dimensions of 1.1 by 7.4 nm and molecular weight of approximately 5kD.

The permeability of gap junctions to siRNA demonstrates a new function, that of facilitating gene silencing from one cell to another. It suggests the potential for a source cell producing a siRNA, to affect gene expression within a syncytium of cells if an appropriate connexin is expressed. Yet, to understand how effective one cell might be in silencing gene activity in neighbouring cells we need to know how far the siRNA can move within a multicellular array. Junctional permeability is one of three important factors that can limit the spread of siRNA throughout a tissue. The other two are synthesis and degradation rates for the siRNA. Figure 2 is a simplified illustration of the role these factors play in the spread of siRNA within a tissue. Of interest is that siRNA from either an endogenous or an exogenous source survives and functions for many hours to days (Aliksy & Davidson, 2004) suggesting that siRNA movement from a source cell to those at distances of even a number of cell diameters away is possible.

siRNA is selective in silencing its gene target and as such presents an ideal therapeutic agent to silence the expression of proteins associated with various disease states in a variety of substrates. Yet to date its therapeutic application has been limited by an inability to deliver the siRNA selectively to the interiors of the target cells. Given our experimental results, the potential for siRNA to be delivered by one cell to a syncytium and affect gene expression in many other cells connected by gap junctions raises the possibility of using siRNA-loaded cells as the platform for a targeted delivery system. We have recently demonstrated that adult human mesenchymal stem cells express connexin 43 (Valiunas *et al*. 2004) and can deliver a pacemaker gene to the cardiac syncytium

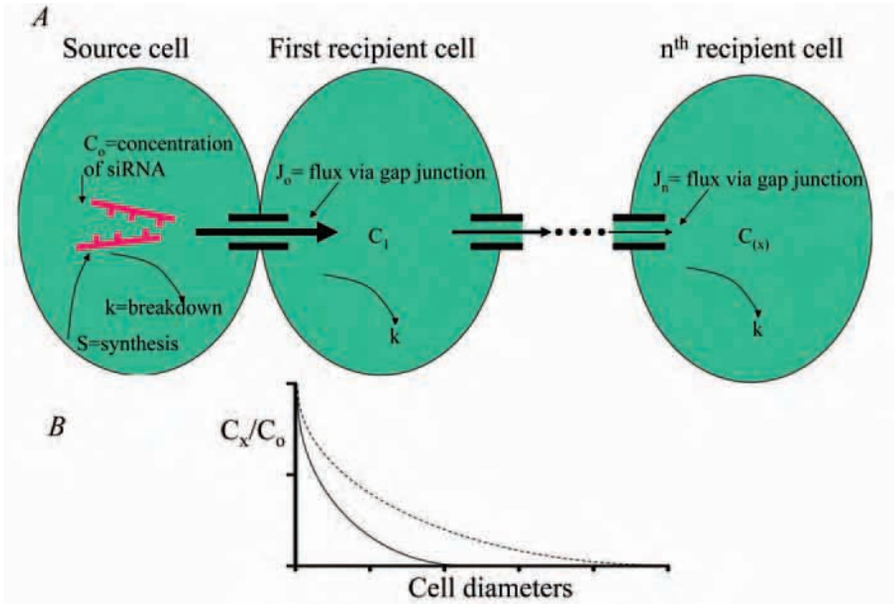


Figure 2. *A*, illustrates a linear array of cells linked by gap junctions where one cell is a source of a specific siRNA, producing that particular species at some rate S (synthesis rate). In all the cells the siRNA is subject to a degradation rate (k). The arrows indicate the transjunctional flux between cell pairs along the array. With distance the concentration, C1, ... C(x), declines and hence the thickness of the arrow is reduced to signify less flux. *B*, illustrates the hypothetical distribution of the siRNA within the array at steady state where the concentration of the siRNA is a constant in the source cell and the subsequent concentrations in adjacent cells are subject to degradation without de novo synthesis in these cells. Two cases are shown with high (solid line) and low (dashed line) degradation rates.

(Potapova *et al*. 2004). These same cells elicited no demonstrable rejection when maintained in canine heart for 6 weeks (Plotnikov *et al*. 2005), suggesting the possibility of their use from allogeneic sources.

In summary, the property of siRNA to permeate gap junction channels composed of connexins opens a door to targeted systemic silencing. How rapidly we avail ourselves of this opening and employ cell-based delivery for siRNA-based therapeutics remains to be seen.

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Working out aerobic fitness

The cardiac and vascular factors that improve endurance performance, aerobic fitness, and exercise capacity are being studied down to subcellular levels in experimental models of exercise training

Clockwise from top right: Ole Kemi, Per Haram, Oyvind Ellingsen and Ulrik Wisloff

In the late 1990s, we combined cellular cardiology and exercise physiology to study the biological causes of why physical activity and exercise training are beneficial in both health and disease. Physical activity and exercise training increases function and prevents disease in the cardiovascular system, improves the outcome in patients with manifest disease and improves the prospects of rehabilitation. In fact, several sets of data strongly suggest that the level of aerobic fitness, as determined by metabolic equivalents or maximal oxygen uptake ($\dot{V}O_{2max}$), directly links to health and survival prospects, even when traditional risk factors are present or the patient is on conventional medical treatment (Myers *et al*. 2002, O'Neill *et al*. 2005). It is clear that changes originating from the cell or molecule of the heart and artery must accompany and possibly explain the beneficial effects.

Thus, we established experimental models to study research questions pertaining to biological mechanisms of fitness and health (Kemi *et al*. 2002, Wisloff *et al*. 2001). Today, the guidelines regarding exercise training as a therapeutic approach need refinement and fine-tuning. An important aspect is therefore that exercise and the effects on exercise capacity must be controlled, in terms of measuring $\dot{V}O_{2max}$ accurately and in terms of how much exercise is performed causing the outcome. An intensity-controlled treadmill model is currently the only suitable model allowing this. Custom-made treadmills with metabolic chambers for both mice and rats were found to be reproducible for measuring oxygen uptake ($\dot{V}O_2$) over a range of running intensities. Also, ramp test protocols for measuring $\dot{V}O_{2max}$ were established; highest values obtained at or around 25º inclination indicated that inclined running is necessary to provoke $\dot{V}O_{2max}$. Moreover, a good agreement between heart rate and $\dot{V}O_2$ up to maximal levels during running to exhaustion; but with maximal heart rate occurring after $\dot{V}O_{2max}$, and several-fold elevated blood lactate levels (peaking at 6-7 mM) and respiratory exchange ratios above 1.05 when reaching $\dot{V}O_{2max}$, strongly suggest that the animals were running to exhaustion, and that $\dot{V}O_{2max}$ was assessed validly. Thus, the current procedures for assessing $\dot{V}O_2$ and $\dot{V}O_{2max}$ by large resemble common protocols used by applied exercise physiology laboratories and clinical services working up athletes as well as patients. For instance, respiratory exchange ratios and blood lactate levels as described above suggest that the individual, whether it be man or mouse, is exercising above the aerobic window and well into where anaerobic metabolic processes kick in. These are therefore common criteria used to determine whether or not a 'true' $\dot{V}O_{2max}$ is reached.

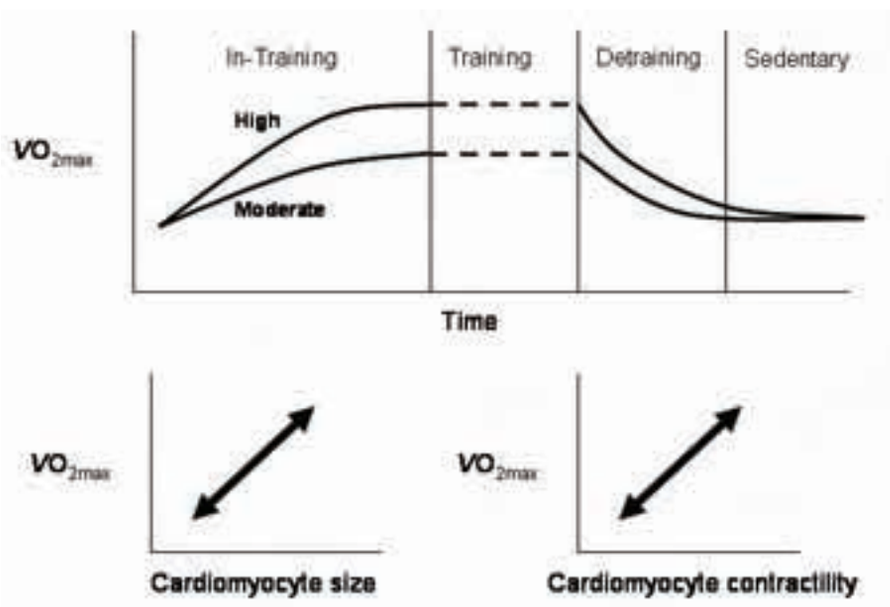

Figure 1. Effects of regular exercise training on $\dot{V}O_{2max}$ and the cardiomyocyte.

Next, we investigated the effects of prolonged high-intensity (85-90% of $\dot{V}O_{2max}$, 5 days/week) interval exercise training on the heart and artery, or the cells that make up those organs (Kemi *et al*. 2002, 2004, 2005, Wisloff *et al*. 2001). As $\dot{V}O_{2max}$ was measured in each animal every week, the running speed was continuously adjusted to maintain the relative training intensity individually. 8-10 weeks of regular training improves $\dot{V}O_{2max}$ by ~50-70%; slightly more in rats than mice. Correspondingly, maximal aerobic velocity, i.e. the running velocity where $\dot{V}O_{2max}$ was reached, improved similarly. Moreover, the running economy, measured as the cost of oxygen to run at a certain speed, was

reduced by ~20% during submaximal running velocities, whereas the respiratory exchange ratio was reduced by ~5% at those velocities. As for the heart, right and left ventricular masses increased 20-30%, which was supported by echocardiography recordings, whereas left ventricular cardiomyocytes increased in size by ~20%, due to proportional cell length and width increase. Cell contractile function, measured at physiological electrical stimulation frequencies, also improves after exercise training; the magnitude of shortening increased 30-40%. In rats, this appears to be largely explained by improved Ca^{2+} sensitivity, rather than by more Ca^{2+} being available to the myofilament machinery, as is the case in mice (unpublished data). Detailed studies of the myofilament responsiveness to given free [Ca^{2+}] in permeabilized cells support our data that less Ca^{2+} is needed to evoke the same response after training in rats (Diffee *et al*. 2001). Myocytes from the hearts of trained animals also contract and relax more quickly than those from untrained animals, which coincides with a more rapid increase and decay of the [Ca^{2+}] transient. Taken together, the structural and functional adaptations of the cardiac muscle cell to long-term exercise explains at least partly why whole-heart function in trained athletes is better than in untrained; increased stroke volume and cardiac output being hallmarks of vigorous exercise over months and years. The cellular findings also provide possible reasoning for better diastolic filling of the ventricles and the concept of athlete's heart.

With increased cardiac output, the artery needs to accordingly secure sufficient conductance of blood to the skeletal muscles. One way of doing so would be increasing the arterial structural diameter permanently, but an alternative way is to improve the vasodilatory capacity. The main vasorelaxive messenger is nitric oxide (NO), which when released from the endothelial cell ultimately reduces intracellular [Ca^{2+}] in the smooth myocyte, causing relaxation. This pathway is stimulated by acetylcholine that speeds up NO production in the endothelium. We find that regular exercise training improves endothelial function, as the acetylcholine concentration evokes half-relaxation decreased ~4-fold in trained animals. There was no difference with an exogenous NO donor (nitroprusside) or after blocking NO synthase (L-NAME), adding further weight to the argument.

Given that regular exercise training considerably affects the morphology and physiology of the cell, we moved on to study the plasticity of the changes, by intervening with different exercise training programs. We compared the effects of high (85-90% of $\dot{V}O_{2max}$) vs. moderate (65-70%) intensity exercise, where 1 hour was allocated to exercise per day, 5 days/week (Kemi *et al*. 2005). Moderate intensity increased $\dot{V}O_{2max}$ only ~half as much as high intensity, paralleled by similar reductions in the magnitude of changes on cardiac myocyte size, fractional shortening, Ca^{2+} sensitivity, and time-courses of the contraction-relaxation cycle and the [Ca^{2+}] transient. Thus, the exercise-induced adaptations in the cardiac myocyte depend upon intensity of exercise. Artery endothelial function had a slightly different dose-response relationship. Acetylcholine-mediated NO-dependent vasoreactivity increased with exercise, and reached near-maximum level of adaptation with moderate exercise, and only a trend for higher sensitivity was observed between moderate and high intensity.

In a different study (Kemi *et al*. 2004), we investigated the time-course of adaptations during training and detraining, that is, how quickly do the changes occur when a high-intensity exercise program is implemented, and how quickly do the effects vanish after withdrawing regular exercise? Whereas it takes about 8-10 weeks of training for $\dot{V}O_{2max}$, cardiac myocyte size, contractile function and Ca^{2+} handling to adapt, most of these effects vanish very quickly when regular exercise is stopped. After regular exercise training for 10 weeks, half the increase in $\dot{V}O_{2max}$ was lost within 2 weeks, most of the effects on cardiomyocyte structure and function disappeared within 2-4 weeks, and arterial improvement was completely lost within 2 weeks of detraining. Thus, exercise-induced beneficial adaptations appear vulnerable; what takes months to improve, only takes weeks to lose again if not properly maintained.

The rigorous control of exercise intensity and volume, as well as adaptations, in terms of $\dot{V}O_{2max}$ is unprecedented in experimental studies; with this scheme, exercise training moves from 'physical activity' to an entity in which responses may be correlated to dose, or the cellular and molecular adaptations may be correlated to changes in $\dot{V}O_{2max}$ or overall, whole-body function. We conclude that aerobic fitness is closely related to cardiomyocyte contractile capacity and acetylcholine-mediated endothelial function, and that the magnitude of training-induced adaptations depends on exercise intensity.

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Erythropoietin controls ventilation in hypoxia

The presence of erythropoietin in blood and brain increases the ventilatory response of mice exposed to oxygen deprivation. Expression of the Epo receptor in the respiratory centre as well as in the carotid bodies suggests that Epo controls the hypoxic ventilatory response at the central (brainstem) and peripheral (carotid body) level

Erythropoietin (Epo) does far more than 'just' increasing red blood cell number. Originally discovered as a 'blood hormone' and widely applied to anaemic patients, Epo has the potential to become a multipurpose drug. It all began back in 1993, when Ryuzo Sasaki and his Japanese co-workers reported the presence of a functional Epo receptor in rat pheochromocytoma PC12 cells, an established cell line with neuronal characteristics (Sasaki *et al*. 2001). A few years later Sasaki's research team, as well as our own, demonstrated that Epo and its receptor are both expressed in the mammalian brain, including human, and that cerebral Epo is expressed in an oxygen-dependent manner. Considering that the blood-brain-barrier cannot be crossed by Epo, we predicted a local function of Epo in the brain upon binding to its receptor, but which one(s)?

Above, left: Max Gassmann, Omolara Ogunshola and Jorge Soliz; Above, right: Max Gassmann with Ryuzo Sasaki; Right: Joseph Vincent

Several elegant experiments performed by various teams on different rodent models of stroke revealed that Epo exerts a protective function upon experimentally-induced brain ischemia. As early as 2002, Hannelore Ehrenreich and her team from Göttingen (Germany) published the first, and so far unique, report on Epo's neuroprotective function in man. Application of recombinant human Epo (rhEpo) in stroke patients was beneficial when given within eight hours of the ischemic insult (Ehrenreich *et al*. 2002). Apart from the tendency to reduce the infarct volume, several clinical tests indicated that Epo-treated patients recovered better and faster compared to the saline-treated control patients.

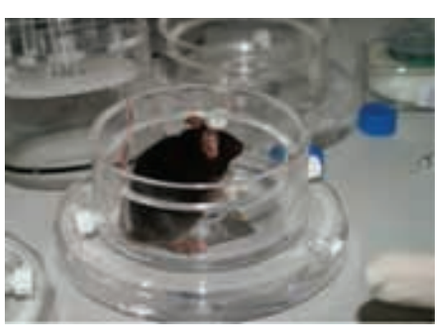

Figure 1. A mouse in a plethysmograph.

Because Epo has neuroprotective effects, we and others tested the impact of rhEpo on other neuronal tissues such as the spinal cord and the retina (reviewed in Gassmann *et al*. 2003). As predicted, we observed that the Epo receptor is also expressed in the retina. Surprisingly, an increased level of Epo in the retina was beneficial as it prevented mice from light-induced retinal degeneration (Grimm *et al*. 2002). Epo's protective effects are even more widespread, as it has been shown by different teams that Epo exerts beneficial effects when applied in several animal models of heart infarct. Moreover, we very recently reported that Epo has protective effects on gentamicin-induced auditory hair loss (Monge *et al*. 2006).

Interestingly, all reports on Epo's non-erythropoietic functions point towards a protective effect of this cytokine upon injury (mostly ischemia). We considered that Epo might also exert a physiological function, and indeed it does; Epo controls the hypoxic ventilatory response (HVR) in mice. During physiological hypoxia (as occurs at high altitude), pulmonary ventilation and arterial oxygen content are elevated by two complementary systems: the neuronal respiratory response (elaborated through the central and peripheral nervous system) leading to increased minute ventilation thereby increasing tissue oxygenation, and the renal-derived Epot that activates erythropoiesis in the bone marrow, thus augmenting the blood's oxygen carrying capacity. Very recently we reported for the first time that these two systems do crosstalk via Epo (Soliz *et al*. 2005).

Carotid bodies are sensory organs whose stimulation by hypoxia activates a chemoreflex pathway. The sensory information is relayed to brainstem neurons that in turn modulate compensatory ventilatory adjustments. Carotid bodies are among the most vascularized organs in the body and are mainly stimulated by the decline of PaO_2. As PC12 cells mimic carotid body type I cells, we hypothesized that these peripheral chemoreceptors might be also activated by Epo. To address this question we placed the animals into a plethysmograph (Fig. 1) and measured HVR in wild type mice upon injection of 2000 U/kg rhEpo. Epo-injected animals showed higher respiratory frequency but lower tidal

volume than saline-injected controls when exposed to severe hypoxia (6% O_2). These data suggest that Epo has an impact on carotid body cells, most probably by binding to the Epo receptor. We found a dense staining of EpoR in the carotid body, apparently localized within islets of chemosensitive cells. This observation implies that peripheral chemoreceptors can be activated by circulating Epo.

We also suspected that brain-derived Epo modulates ventilation by interacting with brainstem respiratory neurons. To test this hypothesis we used a transgenic mouse line (termed Tg21) that constitutively overexpresses human Epo in brain but shows normal Epo plasma levels (Wiessner *et al*. 2001). Tg21 mice showed improved ventilatory response to severe acute hypoxia and improved ventilatory acclimatization to chronic hypoxic exposure. Interestingly, following bilateral transection of the carotid sinus nerves that uncouple the brain from the carotid body (e.g chemodenervation), Tg21 mice adapted their ventilation to acute severe hypoxia while chemodenervated wild type (WT) animals developed a life-threatening apnoea (Fig. 2).

These results imply that Epo in the brain modulates ventilation. Immunohistochemical analysis revealed expression of the Epo receptor in the brainstem's respiratory centres. Additionally, we also provided evidence that Epo modulates breathing control by alteration of catecholaminergic metabolism in brainstem. Taken together, these observations indicate that brain-derived Epo is a key player that modulates neural respiratory control by acting on the central nervous system.

In summary, we have demonstrated that high Epo levels in brainstem respiratory neurons improve ventilatory response and acclimatization to hypoxia. Furthermore, a link between Epo and respiratory control is provided through the peripheral nervous system by the carotid bodies that express the Epo receptor. In other words, Epo is a multifunctional signalling molecule physiologically acting on red blood cell production and lung ventilation to improve the net oxygen inflow to tissues and cells.

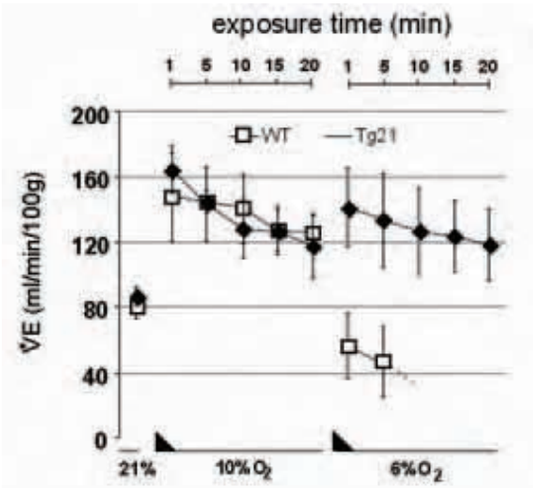

Figure 2. Hypoxic ventilatory response after bilateral transection of the carotid sinus nerve (chemodenervation) in WT and Tg21 mice. The graph shows ventilation (VE) under normoxia (21% O_2), mild hypoxia (10% O_2) and severe hypoxia (6% O_2). Both chemodenervated mouse lines increased ventilation at mild hypoxia due to an increased respiratory rate. However at severe hypoxia, while chemodenerved WT mice showed a very pronounced respiratory depression, chemodenervated Tg21 maintained elevated ventilation. WT mice had to be removed from the plethysmographic chamber after 5-10 min of severe hypoxia (6% O_2). The closed triangle indicates 15 minutes of gradual reduction of FIO_2. *p<0.01. Animals per group = 6-7 (from Soliz *et al*. 2005).

In considering the millennial population of high altitude dwellers, an obvious question arises regarding the impact of plasma and cerebral Epo in the ventilatory adaptation to high altitude. Do high altitude inhabitants have higher concentration of Epo in neural tissue? Does systemic Epo in high altitude dwellers enhance stimulation of carotid body functions? In keeping with this, high altitude de-adaptation syndrome is inherent in highlander populations. In patients suffering from so-called chronic mountain sickness, hypoventilation is associated with excessive erythrocytosis, suggesting that the connection between ventilation and Epo signals is failing. Consequently, the question about the implication of neural and plasma Epo in chronic mountain sickness has to be answered.

Finally, Epo is on the doping list because it augments the blood's oxygen carrying capacity and thus the oxygen delivery to tissue. Considering that an increased level of plasma Epo stimulates carotid bodies under hypoxic conditions, it is tempting to speculate that Epo-mediated improved performance in athletes is also partially due to enhanced ventilatory and/or sympathetic capacity.

Obviously, Epo will keep us all very busy, as the 'old' drug has many 'new' functions that await detailed investigation.

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Bursting with currents

Vasopressin secretion varies with serum osmolality. We have identified a new osmosensitive current that may alter the firing patterns of the cells that release this important hormone

Wenbo Zhang (top) and Thomas Fisher

When the osmolality of our blood increases, our magnocellular neurosecretory cells (MNCs) start to burst (electrophysiologically speaking, that is). These neurones fire few action potentials when our blood is hypo-osmolar, but progressively increase their rate of firing as the osmolality increases (Bourque & Oliet, 1997). This is part of an important homeostatic mechanism that maintains our body fluid balance because these cells release either vasopressin (VP), which causes the retention of water in the kidneys, or oxytocin (OT), which causes (in some species) excretion of sodium. The release of these two hormones into the circulation is increased as the firing rate of the MNCs is increased. VP-releasing MNCs, furthermore, adopt a pattern of firing composed of bursts of action potentials lasting tens of seconds alternating with rest periods of roughly equal length. This pattern of firing, known as phasic firing, maximizes VP release.

The electrophysiological mechanisms underlying the osmosensitive changes in firing rate and pattern are incompletely understood. Although some of the increase in firing rate is due to an increase in excitatory inputs onto the MNCs, the MNCs are also inherently osmosensitive. Patch clamp experiments have shown that the MNC cell bodies express non-selective stretch inactivated cation channels (SICs) whose activity is determined by osmotically-evoked changes in cell volume (Oliet & Bourque, 1993). When exposed to hypo-osmolar solutions, the MNCs stretch, causing the SICs to close. When the external solution is hyper-osmolar, however, the MNCs shrink, which relieves the membrane tension and allows the SICs to open. This allows cations to flow into the cell, causing it to depolarize and become more responsive to excitatory inputs. This process is central to explaining how the MNCs increase their firing rate in response to increases in osmolality.

The initiation of a burst depends on a Ca^{2+} dependent depolarizing afterpotential (DAP) that is activated by action potentials and that increases the likelihood of subsequent action potentials (Roper *et al.* 2004). The amplitude of the DAP summates during repetitive firing, leading to the sustained depolarization that underlies the phasic burst. Ca^{2+} dependent K^+ currents are also activated by action potentials and these currents may be involved in slowing firing during a burst. Although activation of Ca^{2+} dependent currents is known to terminate bursts in other types of neurons, they do not appear to play such a role in MNCs. Measurements of Ca^{2+} levels during a burst suggest that the activation of Ca^{2+} dependent K^+ currents should be maximized well before the termination of the phasic

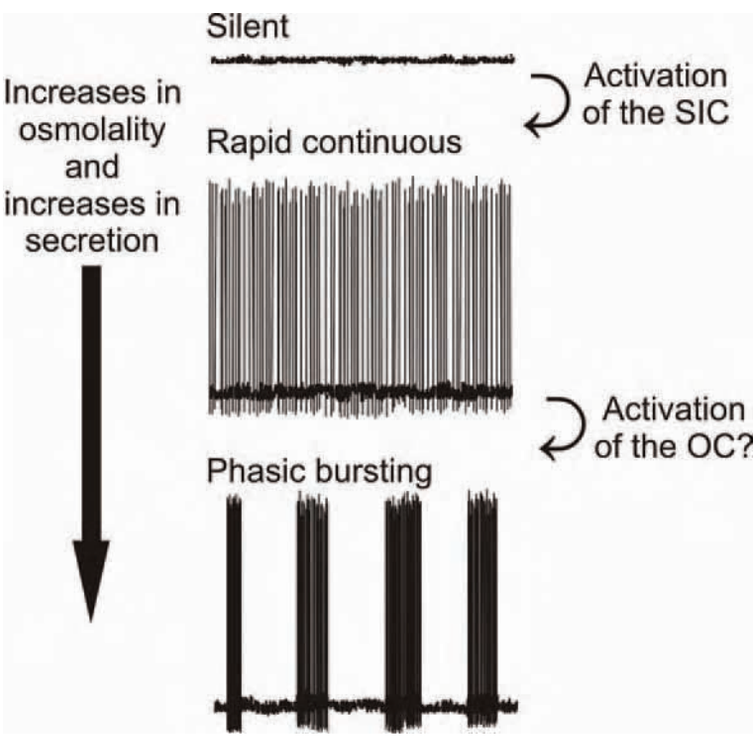

Figure 1. Osmosensitive currents and the regulation of MNC firing. The diagram above illustrates typical patterns of firing exhibited by VP-ergic MNCs in the presence of different external osmolalities. While the MNCs are electrically silent in hypo-osmolar solutions, increases in osmolality cause progressive increases in the firing rate and the eventual adoption of a phasic bursting pattern of firing. These changes are associated with an increase in VP secretion. The activation of the SIC causes depolarization of the MNCs leading to an increase in responsiveness to excitatory inputs and an increase in firing rates. The activation of the OC might be important in mediating the transition to burst firing by inhibiting repetitive firing.

bursts (Roper *et al* 2004). The mechanisms underlying the termination of the long phasic bursts of MNCs are therefore not entirely clear. One current model posits that somatodendritic release of the κ-opioid peptide dynorphin during a burst acts on the MNCs in an autocrine fashion to suppress the DAP, thereby leading to burst termination (Brown & Bourque, 2004).

It is also possible, however, that osmotic activation of a current or currents other than the SIC might be involved in the transition to burst firing. Since MNCs exposed to high osmolality may go through a stage of rapid continuous firing before converting to a phasic firing pattern (Bourque & Renaud, 1984), there may be a separate process that is necessary for the adoption of burst firing. We therefore sought to determine whether there are any other ion channels modulated by changes in osmolality. As reported in the August issue of *The Journal of Physiology*, we recently identified another current in isolated MNCs that increases as a function of osmolality (Liu *et al.* 2005). Unlike the SIC, this osmosensitive current (the OC) is also voltage sensitive and is activated during voltage clamp by steps to potentials greater than -60 mV. Although the amplitude of the OC varies from cell to cell, there is a marked increase in amplitude (approximately two-fold) in greater than 60% of cells tested. The OC is therefore the first voltage gated current identified in the MNCs that is sensitive to osmolality. The slow activation of this current, and the lack of inactivation, suggest that it could increase in amplitude slowly over the course of a burst of action potentials. The OC might thus be expected to influence the MNC firing rate and/or pattern.

The ionic selectivity of the OC has not yet been established, but our evidence suggests that the current may be a K^+ current. Although the current may be carried by Na^+ in the absence of K^+, the addition of even a small quantity of K^+ into the internal recording solution results in block of Na^+ flux. When K^+ is then added to the external solution, voltage steps result in an inward flux of K^+. These data suggest that the OC may be a voltage dependent K^+ current. Pharmacological experiments support this conclusion. The OC can be blocked by either Ba^{2+} or Cs^+ ions, both of which are known K^+ channel blockers. The OC can be activated, however, in the presence of a large concentration of TEA, suggesting that it is relatively insensitive to this K^+ channel blocker.

What could be the function of a K^+ current that turns on as osmolality is increased? It appears paradoxical that a K^+ current would be activated by a stimulus that causes an increase in the output from these cells (i.e. the release of VP). The answer to this question may be that the OC has a role in mediating the transition into phasic bursting. By slowly activating during repetitive firing, the OC might act as a brake that temporarily silences a cell, thereby preparing it to respond to excitatory inputs with another burst of action potentials. Differential activation of the SIC and the OC might contribute to a variety of firing patterns, such as slow irregular or fast continuous firing, or firing in short or phasic bursts.

We have therefore identified an osmosensitive current that is likely to be a K^+ current and that may be involved in the regulation of MNC firing in response to changes in the external osmolality. We are presently trying to identify the current in the hope of finding specific modulators that would help in identifying its physiological role. It remains to be seen whether the OC, like the SIC, is mechanosensitive. Alternatively, the current may be modulated by changes in second messenger systems mediated by changes in osmolality. Further characterization of the OC may help to understand the osmosensitive regulation of VP and OT release and the transitions between firing patterns observed in the MNCs.

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The Journal of Physiology

Brian Robertson (University of Leeds) has been elected as Deputy Editor-in-Chief of *The Journal of Physiology* to replace Prem Kumar in July. Brian is also *The Journal*'s Topical Reviews Editor. Gordon Drummond (Royal Infirmary, Edinburgh) will serve as an additional representative of the Editorial Board on *The Journal of Physiology*'s Executive Committee.

Other Editors currently serving on *The Journal*'s Executive Committee are William Large (Editor-in-Chief), Steven Mifflin (International Editor), George Augustine (Designated Senior Editor), Hugh Matthews (Designated Senior Editor Elect), Peter Ellaway and Chris McBain. The Society is represented by the Chairman of its Executive Committee, the Treasurer and the Chief Executive.

Developing insights into Purkinje cell maturation

Recent evidence reveals a temporal correspondence between the maturation of spike output properties and cell structure during postnatal Purkinje cell development, which further parallels the development of anatomical, synaptic and behavioural indices of cerebellar maturation

The cerebellum coordinates fine motor movements, underlies the adaptation of ocular responses, and supports the learning of some conditioned behaviours (Ito, 1984). However, in the rat and mouse, these behaviours, and the anatomy and physiology that enable these functions, are either absent in the altricial neonate, or present in an immature form (Altman & Bayer, 1997).

At birth the cerebellum is limited to a pair of small masses overlying the fourth ventricle, with Purkinje cells arranged in clusters and granule cells present in an external layer of the cortex. Neuronal morphology is immature, synaptic innervation is rudimentary, and the repertoire of cerebellar-dependent behaviours is limited (Altman & Bayer, 1997). By the third to fourth postnatal weeks the anatomy, synaptic connectivity and neuronal morphology, as well as behavioural indices of cerebellar function, all reach adult levels (Altman & Bayer, 1997). The development of these characteristics is known with precise temporal resolution. However, the development of intrinsic neuronal properties, such as spike output patterns, and any relationship to the development of cell morphology, had not been determined with high temporal resolution for any cerebellar cell type.

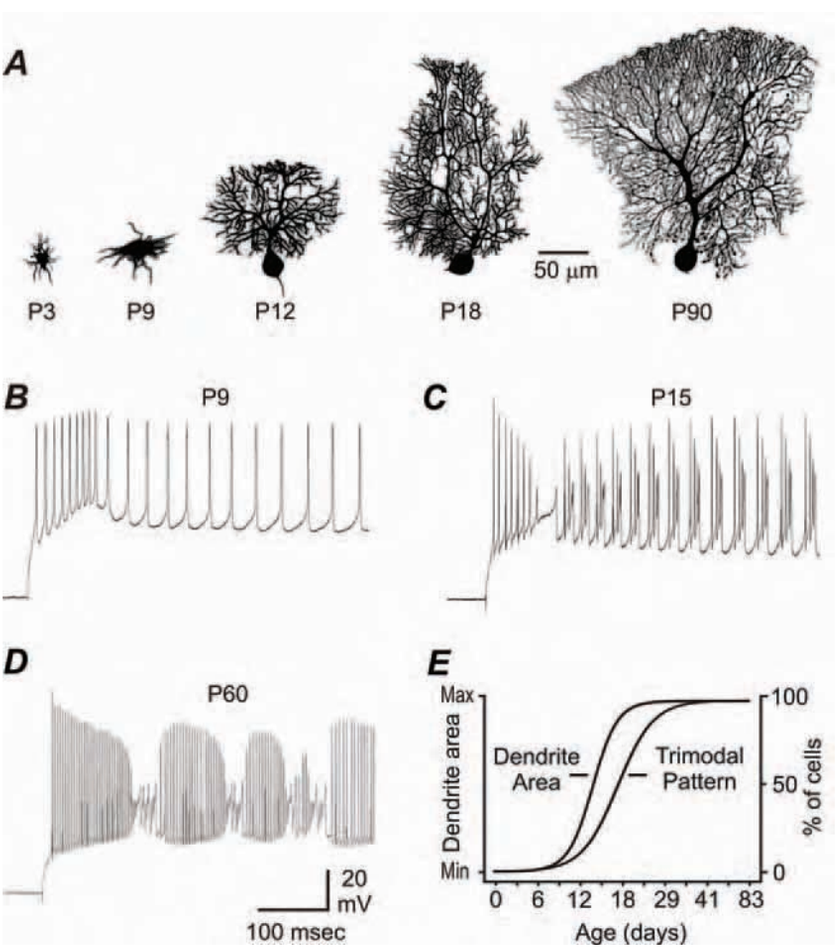
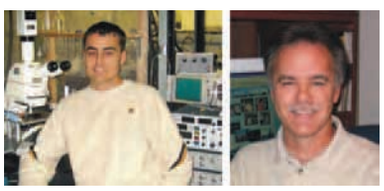


Figure 1. Development of Purkinje cell structure and function. *A*, Purkinje cell morphology from P3 to P90. *B-D*, evoked spike output for an immature (P9), intermediate (P15) and adult (P60) Purkinje cell. *E*, Superimposed Boltzmann fits for the development of Purkinje cell dendrite area and percentage of cells generating the trimodal pattern of spontaneous spike output. All panels adapted from McKay & Turner (2005).



Bruce McKay (left) and Ray Turner

To this end we studied the structural and functional development of Purkinje cells, a cell type of central importance to overall cerebellar function, from P0 through P90 using whole-cell patch clamp recordings and Neurobiotin cell fills in the *in vitro* slice preparation (McKay & Turner, 2005). We found that both morphological and electrophysiological characteristics develop with a sigmoidal time course: an initial stable immature stage of minimal change from P0 to ~P9, a transition stage from >P9 to ~P18 wherein the conversion from immature to adult characteristics occurs, and finally a stable adult stage >P18 where only minor refinements are noted (McKay & Turner, 2005). For instance, during the stable immature stage Purkinje cells possess a peri-somatic dendritic configuration (e.g., P3 and P9, Fig. 1*A*). During the transition stage Purkinje cells retract their peri-somatic dendrites and then generate a single primary stem dendrite that rapidly increases in surface area to nearly adult levels (e.g., P12 and P18, Fig. 1*A*). During the stable adult stage only small morphological changes are observed (Fig. 1*A* and 1*E*).

Occurring alongside morphological changes is a parallel shift in the patterns of evoked and spontaneous spike output. Throughout the stable immature stage intracellular stimulation evokes a transient low threshold burst discharge of action potentials (Fig. 1*B*). However, during the transition stage Purkinje cells proceed through an under-developed form of repetitive high threshold bursts (Fig. 1*C*), which ultimately matures to a stable adult

pattern of high threshold burst output (Fig. 1*D*). Following a similar time course, the percentage of cells generating the trimodal (tonic, burst, quiet) pattern of spontaneous output is 0% throughout the stable immature stage and quickly increases to nearly 100% by the end of the transition stage (Fig. 1*E*). Co-plotting the Boltzmann fits (see McKay & Turner, 2005) of the developmental changes in dendritic surface area and the proportion of Purkinje cells generating the trimodal pattern reveals the relative postnatal time courses for these two variables. This strategy indicates that dendritic development precedes the development of trimodal output by a few days, but importantly reveals that, once initiated, these characteristics mature at similar rates.

Interestingly, the time courses of multiple aspects of cerebellar development, including the maturation of gross anatomy, synaptic innervation and behavioural indices appear to parallel the time course of development we describe for Purkinje cell structure and spike output.

For instance, one measure of gross anatomy – the cross-sectional area of the vermis – changes minimally during approximately the first postnatal week (stable immature stage), undergoes a massive expansion to adult size over the next two weeks (transition stage), and then plateaus in area (stable adult stage) (Altman & Bayer, 1997). Also following a sigmoidal time course is the development of synaptic inputs to Purkinje cells. Throughout the first postnatal week only a small number of Purkinje cell parallel fibre and basket cell synapses are detected, whereas a marked proliferation is noted during the second postnatal week with the attainment of stable adult levels by the third postnatal week (Larramendi, 1969). Further, the number of climbing fibres that synapse onto each Purkinje cell is stable at 3-4 during the first postnatal week, decreases to one climbing fibre per Purkinje cell during the second postnatal week, and remains stable at this level throughout adulthood (Scelfo & Strata, 2005). Finally, the maturation of known cerebellar-dependent behaviours, including pelvis elevation, maintaining balance on a narrow plank, mid air righting, and rearing without support, are essentially absent during the first postnatal week, improve significantly during the second and third postnatal weeks, and stabilize at adult values by the fourth postnatal week, further mirroring the development of Purkinje cell characteristics (Altman & Bayer, 1997).

Thus despite the diversity of these anatomical, synaptic, cellular and behavioural indices, the temporal progression towards adult-like character follows a similar sigmoidal time course – each characteristic begins with an initial stage of stable immaturity persisting for approximately the first postnatal week, rapidly progresses through a transition stage over the course of only approximately one week, and then persists in a stable adult stage.

The use of Boltzmann functions to analyze a range of developmental variables may prove useful in establishing a comprehensive and quantitative picture of multiple aspects of postnatal cerebellar development.

Acknowledgements

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Joint International Meeting of the German Physiological Society and the Federation of European Physiological Societies (FEPS)
Munich, Germany
26–29 March 2006

From the top: Bavarian Evening; Ludwig-Maximilians-Universität; visitors to the Blackwell Publishing/*Journal of Physiology* stand – Lutz Pott (former *Journal* Editor) and Bernhard Becker from the local organising committee. (photos by Mary Wilson and Sue Ecob who represented *The Journal of Physiology*).

Muscle mass at the top: a likely role for fibre hyperplasia in humans

The extreme increase in muscle mass observed after heavy resistance training cannot be simply explained on the basis of muscle fibre hypertrophy, as is commonly assumed

Giuseppe D'Antona

The increase in skeletal muscle mass in response to several stimuli including intense physical exercise is considered an obvious example of cell plasticity. The accepted mechanism underlying such changes is quantitative modifications of gene expression.

In skeletal muscle each gene can be upregulated or downregulated in response to several factors including mechanical load (exercise), neural discharge and hormones. Gene products can be quantitatively modified and new functional and structural features can appear at macroscopic level. In particular, the 'quantitative mechanism' of muscle plasticity seems to be the major accepted factor by which skeletal muscle can adapt to variable functional requirements through changes in mass and fibre size (hypertrophy). Quantitative changes of fibre size are also commonly considered as the major determinants of load-induced changes in muscle force generation.

The foremost factor shaping muscle phenotype through the quantitative mechanisms is exercise resistance training (Fig. 1). Resistance training has been extensively studied and is well known to stimulate muscle hypertrophy.

Interestingly, the level of muscle mass hypertrophy described in various works appears to depend on the experimental design of the study. In fact comparative studies of different subjects populations (cross-sectional studies) have shown higher but comparable degree of muscle hypertrophy (MacDougall *et al*. 1982; D'Antona *et al*. 2006), whereas longitudinal studies of shorter (2-14 weeks) duration have shown much lower degree of hypertrophy (Aagaard *et al*. 2001).

It is generally assumed that the increase in muscle mass following resistance training can be fully accounted for by individual muscle fibre hypertrophy and hypertrophic response appears to be fibre-type specific. Whereas hypertrophy clearly spares slow fibres, it selectively involves fast fibres (Aagaard *et al*. 2001; D'Antona *et al*. 2006). The cause of such fibre-type selectivity is unclear and requires future investigations.

The mechanism by which heavy work increases muscle mass, through the increase of fibres size, may be the activation of protein synthesis pathways. The expression of Insulin-like Growth Factor-I (IGF-I), induced by muscle overload, and insulin have been demonstrated to be responsible for regulation of protein synthesis by stimulating the Phosphoinositide 3'-Kinase/Protein Kinase (PI3K/Akt) pathway, which in turn results in the downstream activation of targets required for protein synthesis. Recently it has also been demonstrated that activation of Akt is able to induce an increase in muscle mass through a dramatic increase in fibre size of individual fibres (Glass, 2005).

Notwithstanding an undoubted role of fibres hypertrophy, the traditionally accepted quantitative mechanism of muscle plasticity is not fully able to explain the observed changes in muscle mass due to resistance exercise. In fact, studies performed on resistance athletes have shown a wide range of muscle hypertrophy without a strict correlation with changes in fibre size. This observation is most clear when considering the few available studies on body builders. These reported only limited hypertrophy of muscle fibres, failing to account for the obvious and extreme hypertrophy of whole muscles (MacDougall *et al*. 1982; Tesch & Larsson, 1982).

The observed discrepancy between the mean fibre cross sectional area and the anatomical cross sectional area (CSAanat, cross sectional area of a muscle determined in a plane axial to the long axis of a muscle) of the muscle determined by MRI clearly suggests that hypertrophy cannot fully explain the observed hypertrophy of whole muscle (MacDougall *et al*. 1982; Tesch & Larsson, 1982).

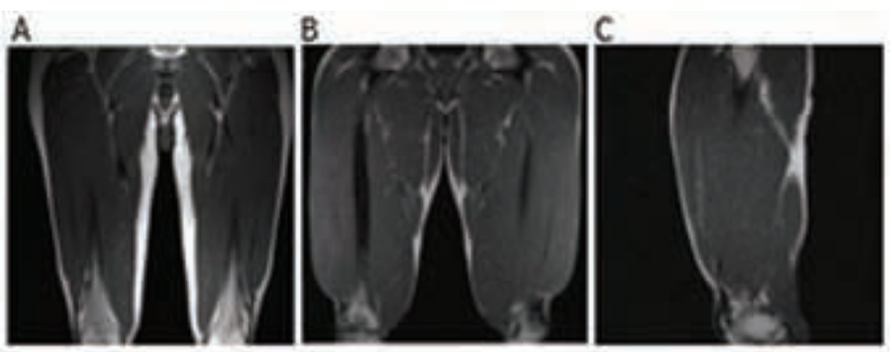

Figure 1. Coronal (A, B) and sagittal (C) magnetic resonance images (MRI) of the thigh of a normally active subject (A) and a body builder (B, C) highlight dramatic increase of skeletal muscle mass following long term heavy resistance training (modified from D'Antona *et al*. 2006).

Which mechanisms underlie such discrepancy?

Which other phenomena than fibres hypertrophy contribute to the striking increase in muscle mass due to long-

CSAp ($m^2 \cdot 10^{-3}$)	
Body builder	17
Control	6
Ratio	2.5

Table 1. Physiological cross sectional area (CSAp) of the vastus lateralis of a body builder and a control normally active subject (D'Antona G unpublished observation).

term and very high intense resistance training in humans?

In a recent study we aimed to help answer this question by investigating if changes in muscle architecture may explain the difference between mean fibre area and CSAanat observed in elite male body builders.

It is known that the relation between the physiological CSA (CSAphysiol, cross sectional area of a individual muscle fibres of a muscle, Table 1), and the anatomical CSA (CSAanat) is not constant. The latter relation varies according to the pennation angle, which is the angle between the axis of the fibres and the axis of the muscle (Narici *et al*. 1996). Physical exercise is known to induce significant adjustments of the spatial orientation of the muscle fibres. This varies the pennation angle, which has been found to increase following resistance training and to be larger in body builders than in controls (Kawakami *et al*. 1995). An increase in the pennation angle has thus been considered as a possible source of the discrepancy between CSAphysiol and CSAanat.

In our work, we considered known values of pennation angle and measured values of CSAphysiol and CSAanat of the vastus lateralis of elite body builders and untrained subjects. By applying these values to a simple theoretical model of muscle architecture, we excluded the idea that such differences could be entirely attributed to differences in pennation angle between the two groups of subjects (D'Antona *et al*. 2006).

These results combined with the observation of signs of muscle regeneration (the appearance of a low percentage of neonatal myosin isoforms) allowed us to hypothesize that hyperplasia represented the most feasible mechanism, overlapping with the increase in fibres size, leading to the observed increase in muscle mass after chronic heavy resistance training.

Unfortunately, to date, only indirect observations like ours support this hypothesis in humans. In animal models (rat or chicken) some evidence does suggest that hyperplasia can occur in overloaded conditions or after stretching.

The possible mechanisms involved in exercise-induced muscle hyperplasia are only partially known. It has been demonstrated that muscle overload induces new fibre formation resulting from satellite cell activation, proliferation, differentiation and fusion, similar to what happens during development (Tamaki *et al*. 1997). It is unclear to what extent satellite cell proliferation and fusion arise within the exercised muscle and the fibre injury appears the origin of the regenerative response. In both rats and chickens subjected to muscle overload there is evidence that cells formed *de novo* may arise in interstitial tissue between existing fibres (Fig. 2).

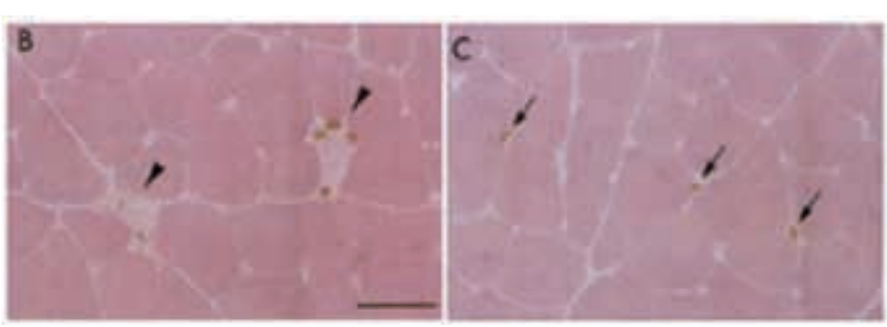

Figure 2. Cross sections of rat plantaris muscle after resistance exercise training demonstrate the appearance of degenerating cells (arrowheads in Panel B) as well as regenerating cells at the periphery of normal fibres (arrows in Panel C). (with permission from Tamaki T *et al*. 1997).

Regarding the possible signals involved in activation of quiescent satellite cells, a number of extracellular factors are known to be involved in muscle regeneration that is triggered in response to muscle injury. Some of them (Myogenic Transcription Factors, MRFs, IGF; Fibroblast Growth Factors, FGF; Hepatocyte Growth Factor, HGF; Sonic hedgehog, Shh and others) are involved in the activation of adult stem cells and in their proliferation, while others (MRFs, IGF, Neuregulin, NRG, Shh, Wingless-Int, Wnt) promote muscle differentiation. Their possible role in determining the hyperplastic response after chronic heavy resistance training deserves further investigation.

Acknowledgments

I am grateful to Marco Narici and Francesca Grisù Caliaro for useful discussions on muscle architecture and regeneration. This work has been supported by a grant from Italian Space Agency (ASI) and World Anti-Doping Agency (WADA).

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Muscle mass at the top: a likely role for fibre hyperplasia in humans

The extreme increase in muscle mass observed after heavy resistance training cannot be simply explained on the basis of muscle fibre hypertrophy, as is commonly assumed

Giuseppe D'Antona

The increase in skeletal muscle mass in response to several stimuli including intense physical exercise is considered an obvious example of cell plasticity. The accepted mechanism underlying such changes is quantitative modifications of gene expression.

In skeletal muscle each gene can be upregulated or downregulated in response to several factors including mechanical load (exercise), neural discharge and hormones. Gene products can be quantitatively modified and new functional and structural features can appear at macroscopic level. In particular, the 'quantitative mechanism' of muscle plasticity seems to be the major accepted factor by which skeletal muscle can adapt to variable functional requirements through changes in mass and fibre size (hypertrophy). Quantitative changes of fibre size are also commonly considered as the major determinants of load-induced changes in muscle force generation.

The foremost factor shaping muscle phenotype through the quantitative mechanisms is exercise resistance training (Fig. 1). Resistance training has been extensively studied and is well known to stimulate muscle hypertrophy.

Interestingly, the level of muscle mass hypertrophy described in various works appears to depend on the experimental design of the study. In fact comparative studies of different subjects populations (cross-sectional studies) have shown higher but comparable degree of muscle hypertrophy (MacDougall *et al*. 1982; D'Antona *et al*. 2006), whereas longitudinal studies of shorter (2-14 weeks) duration have shown much lower degree of hypertrophy (Aagaard *et al*. 2001).

It is generally assumed that the increase in muscle mass following resistance training can be fully accounted for by individual muscle fibre hypertrophy and hypertrophic response appears to be fibre-type specific. Whereas hypertrophy clearly spares slow fibres, it selectively involves fast fibres (Aagaard *et al*. 2001; D'Antona *et al*. 2006). The cause of such fibre-type selectivity is unclear and requires future investigations.

The mechanism by which heavy work increases muscle mass, through the increase of fibres size, may be the activation of protein synthesis pathways. The expression of Insulin-like Growth Factor-I (IGF-I), induced by muscle overload, and insulin have been demonstrated to be responsible for regulation of protein synthesis by stimulating the Phosphoinositide 3'-Kinase/Protein Kinase (PI3K/Akt) pathway, which in turn results in the downstream activation of targets required for protein synthesis. Recently it has also been demonstrated that activation of Akt is able to induce an increase in muscle mass through a dramatic increase in fibre size of individual fibres (Glass, 2005).

Notwithstanding an undoubted role of fibres hypertrophy, the traditionally accepted quantitative mechanism of muscle plasticity is not fully able to explain the observed changes in muscle mass due to resistance exercise. In fact, studies performed on resistance athletes have shown a wide range of muscle hypertrophy without a strict correlation with changes in fibre size. This observation is most clear when considering the few available studies on body builders. These reported only limited hypertrophy of muscle fibres, failing to account for the obvious and extreme hypertrophy of whole muscles (MacDougall *et al*. 1982; Tesch & Larsson, 1982).

The observed discrepancy between the mean fibre cross sectional area and the anatomical cross sectional area (CSAanat, cross sectional area of a muscle determined in a plane axial to the long axis of a muscle) of the muscle determined by MRI clearly suggests that hypertrophy cannot fully explain the observed hypertrophy of whole muscle (MacDougall *et al*. 1982; Tesch & Larsson, 1982).

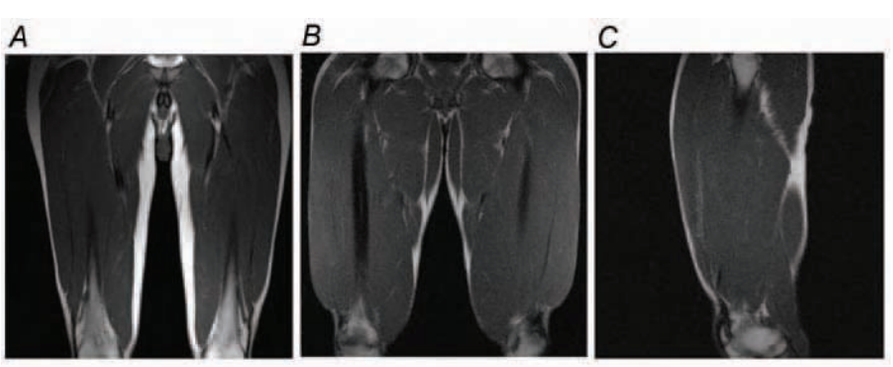

Figure 1. Coronal (*A*, *B*) and sagittal (*C*) magnetic resonance images (MRI) of the thigh of a normally active subject (*A*) and a body builder (*B*, *C*) highlight dramatic increase of skeletal muscle mass following long term heavy resistance training (modified from D'Antona *et al*. 2006).

Which mechanisms underlie such discrepancy?

Which other phenomena than fibres hypertrophy contribute to the striking increase in muscle mass due to long-

	CSAp ($m^2 \cdot 10^{-3}$)
Body builder	17
Control	6
Ratio	2.5

Table 1. Physiological cross sectional area (CSAp) of the vastus lateralis of a body builder and a control normally active subject (D'Antona G unpublished observation).

term and very high intense resistance training in humans?

In a recent study we aimed to help answer this question by investigating if changes in muscle architecture may explain the difference between mean fibre area and CSAanat observed in elite male body builders.

It is known that the relation between the physiological CSA (CSAphysiol, cross sectional area of a individual muscle fibres of a muscle, Table 1), and the anatomical CSA (CSAanat) is not constant. The latter relation varies according to the pennation angle, which is the angle between the axis of the fibres and the axis of the muscle (Narici *et al*. 1996). Physical exercise is known to induce significant adjustments of the spatial orientation of the muscle fibres. This varies the pennation angle, which has been found to increase following resistance training and to be larger in body builders than in controls (Kawakami *et al*. 1995). An increase in the pennation angle has thus been considered as a possible source of the discrepancy between CSAphysiol and CSAanat.

In our work, we considered known values of pennation angle and measured values of CSAphysiol and CSAanat of the vastus lateralis of elite body builders and untrained subjects. By applying these values to a simple theoretical model of muscle architecture, we excluded the idea that such differences could be entirely attributed to differences in pennation angle between the two groups of subjects (D'Antona *et al*. 2006).

These results combined with the observation of signs of muscle regeneration (the appearance of a low percentage of neonatal myosin isoforms) allowed us to hypothesize that hyperplasia represented the most feasible mechanism, overlapping with the increase in fibres size, leading to the observed increase in muscle mass after chronic heavy resistance training.

Unfortunately, to date, only indirect observations like ours support this hypothesis in humans. In animal models (rat or chicken) some evidence does suggest that hyperplasia can occur in overloaded conditions or after stretching.

The possible mechanisms involved in exercise-induced muscle hyperplasia are only partially known. It has been demonstrated that muscle overload induces new fibre formation resulting from satellite cell activation, proliferation, differentiation and fusion, similar to what happens during development (Tamaki *et al*. 1997). It is unclear to what extent satellite cell proliferation and fusion arise within the exercised muscle and the fibre injury appears the origin of the regenerative response. In both rats and chickens subjected to muscle overload there is evidence that cells formed *de novo* may arise in interstitial tissue between existing fibres (Fig. 2).

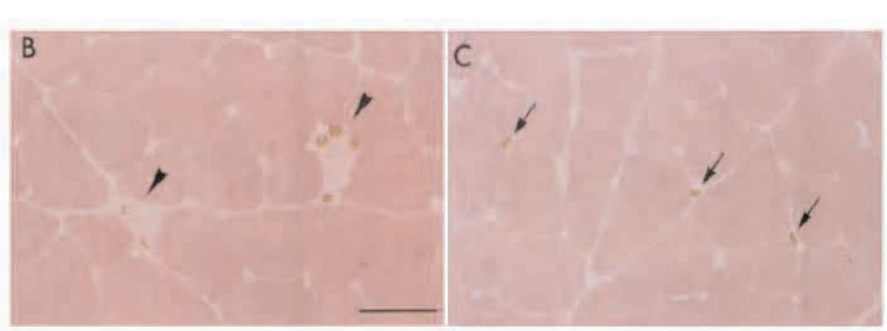

Figure 2. Cross sections of rat plantaris muscle after resistance exercise training demonstrate the appearance of degenerating cells (arrowheads in panel *B*) as well as regenerating cells at the periphery of normal fibres (arrows in panel *C*). (with permission from Tamaki T *et al*. 1997).

Regarding the possible signals involved in activation of quiescent satellite cells, a number of extracellular factors are known to be involved in muscle regeneration that is triggered in response to muscle injury. Some of them (Myogenic Transcription Factors, MRFs, IGF; Fibroblast Growth Factors, FGF; Hepatocyte Growth Factor, HGF; Sonic hedgehog, Shh and others) are involved in the activation of adult stem cells and in their proliferation, while others (MRFs, IGF, Neuregulin, NRG, Shh, Wingless-Int, Wnt) promote muscle differentiation. Their possible role in determining the hyperplastic response after chronic heavy resistance training deserves further investigation.

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Cardiac channelopathies studied with the dynamic action potential clamp technique

Géza Berecki (left) and Antoni van Ginneken

The congenital long-QT syndrome (LQTS) is an inherited disorder that prolongs repolarisation of the ventricular myocyte. It often leads to sudden death from cardiac arrhythmias arising from oscillations during the action potential (AP) plateau, specifically torsades de pointes and ventricular fibrillation. It is a characteristic feature of the cardiac cell membrane that even small changes in individual ionic currents can shift the delicate balance between inward and outward current flow during the plateau and repolarisation and thereby prolong or shorten the AP.

Since the discovery of genetic linkage between cardiac ion channels and the LQTS in the mid 1990s, remarkable results were obtained in understanding various types of this syndrome. At present, most effort has been devoted to documenting the effects of identified mutations on the densities and kinetics of various cardiac ion channels upon heterologous expression. Subsequently, the consequences of channelopathies for cardiac function are inferred by testing the functional effects of the experimentally observed changes with use of mathematical models of cardiac cells (Wehrens *et al*. 2002). However, despite advances in mathematical modeling, the mechanism by which a given genetic defect leads to the clinically observed electrical disease often remains obscure: genetic heterogeneity in LQTS represents a major challenge for modelers as various mutations in the same gene may produce different, often inconsistent functional effects.

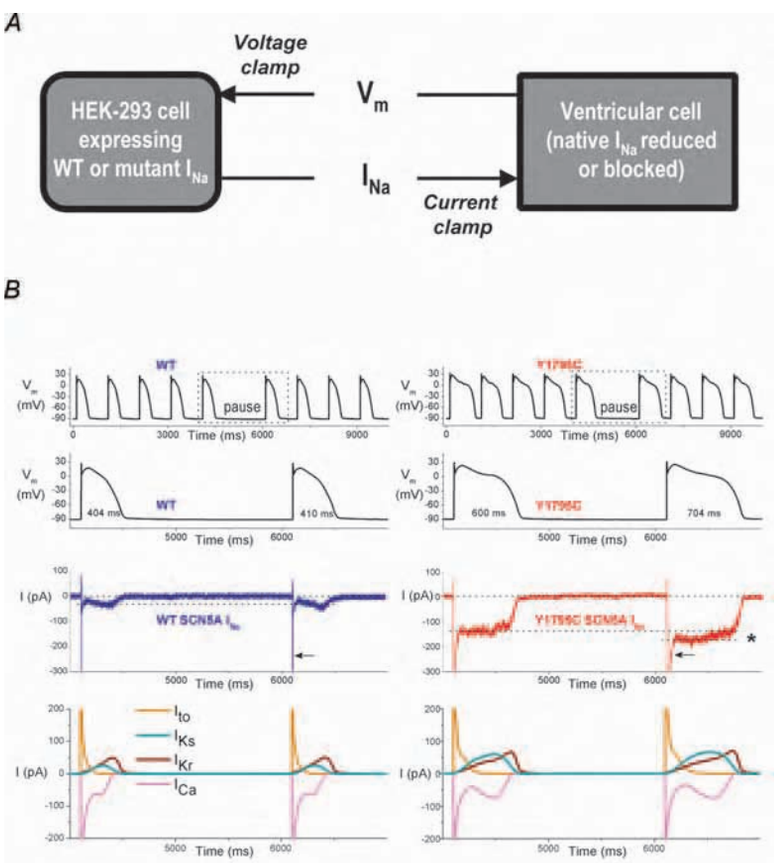

Figure 1. Implementing cardiac sodium current (I_{Na}) in dAPC experiments. *A*, Overall experimental design. I_{Na} from the HEK cell is continuously applied to the ventricular cell as an external current input, partly or entirely replacing I_{Na} in the ventricular cell. *B*, "Model cell mode" dAPC with WT (left) or Y1795C I_{Na} (right). From top to bottom: subepicardial cell APs elicited at 1 Hz before and after a 2-s pause. APs with mutant I_{Na} are prolonged compared to WT. Boxed APs from top traces and associated I_{Na} on expanded time scale. Note that late I_{Na}-increase after the pause is more pronounced with the mutant (asterisk). Dotted line indicate persistent (late) current amplitude, characteristic in type 3 LQTS; peak I_{Na} is off scale (arrows); Relationships between the APs and selected membrane current components of the human ventricular model cell, showing the changes in the time course of transient outward K^+ current (I_{to}), slowly and rapidly activating components of the delayed rectifier K^+ current (I_{Ks} and I_{Kr}, respectively), and L-type Ca^{2+} current (I_{Ca}), along with changes in mutant I_{Na}. Adapted from Berecki *et al*. (2006) with permission from Blackwell Publishing Ltd.

The recently introduced 'dynamic action potential clamp' (dAPC) technique (Berecki *et al*. 2005; 2006) represents an alternative approach to investigate LQTS without making assumptions with regard to (altered) kinetic properties of the studied channel(s). As an extension of the dynamic clamp methodology (briefly reviewed by Wilders, 2005), allows the study of various types of LQTSs (e.g. LQT2 and LQT3, which are linked to mutations in the human ether-a-go-go-related gene, HERG, and sodium channel gene, SCN5A, respectively).

The concept of dAPC is that a selected native ionic current of a ventricular myocyte is effectively replaced with wild-type or mutant current recorded from a transiently transfected human embryonic kidney (HEK)-293 cell. During the dAPC experiment, the ventricular cell and the HEK-293 cell are electrically coupled by means of an electrical circuit. The ventricular cell is in 'current clamp' mode on one patch-clamp setup, whereas the HEK293 cell is in 'voltage clamp' mode on another setup. The command potential for the HEK293 cell is the Vm of the ventricular cell ('action potential clamp'), and the current input applied to the ventricular cell is the current recorded from the transfected HEK293 cell, a connection resulting in dAPC condition.

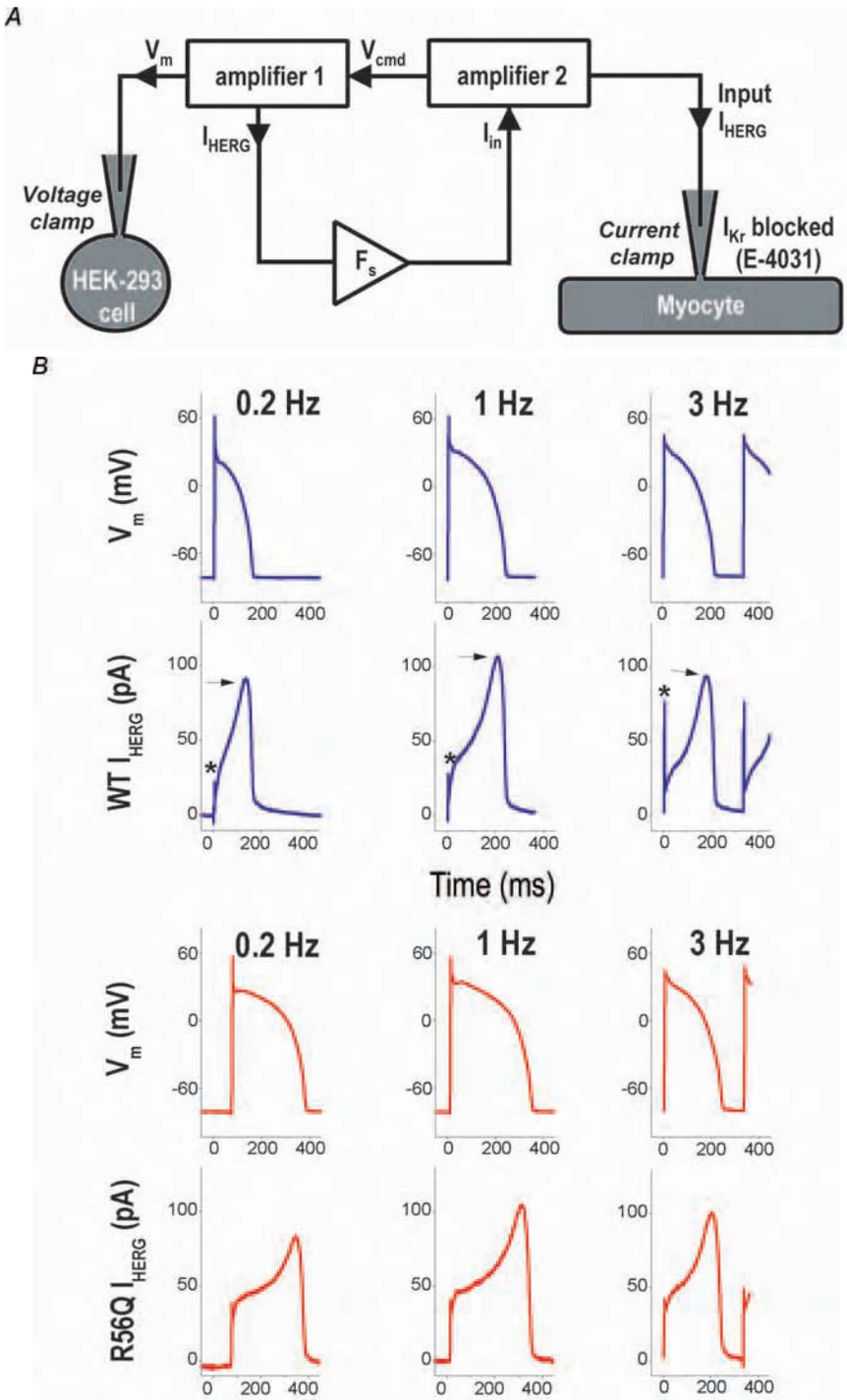

Figure 2. 'Real cell mode' dAPC experiment with WT and mutant HERG current (I_{HERG}). **A,** Diagram of the dAPC technique that is used to effectively replace the pharmacologically blocked native I_{Kr} of a ventricular cell with I_{HERG} from a HEK293 cell. **B,** APs from a myocyte and associated WT (top) or R56Q I_{HERG} (bottom), at different frequencies. The myocyte was successively coupled to HEK-293 cells transfected with WT or R56Q HERG channels. Note the different I_{HERG} waveforms (*, transient I_{HERG}; *arrow*: sustained I_{HERG}) and frequency dependent AP prolongation with R56Q. Adapted from Berecki *et al*. (2005) with the permission of the Biophysical Society (http://www.biophysj.org).

Both a computed model of the human ventricular cell (Priebe & Beuckelmann, 1998) (Fig. 1) or a freshly isolated (real) myocyte (Fig. 2) can effectively be used in dAPC experiments, defining the 'model cell' and 'real cell' modes, respectively. The first offers an outstanding reproducibility of the results, because the implemented (input) wild-type (WT) or mutant current is the only variable during experimentation. Moreover, it allows 'generation' of subendocardial, midmyocardial (M), and subepicardial ventricular cells by adjusting selected membrane ionic currents in the ventricular model cell. Equally, the technically more difficult real cell mode reveals AP waveforms and ion channel kinetics that can be considered close-to-physiological.

The dAPC approach allows rapid and unambiguous determination of the effect(s) of ion channel mutation on the ventricular AP morphology. During experiments, the (altered) shape of the AP directly reflects the effect of a mutation; the frequency dependence of the AP durations, the consequence of a pause on AP morphology as well the arrhythmogenic nature of LQT-associated mutations can be determined, and special kinetic features of cardiac channels can be revealed. With adequate scaling adjustments and procedures to reduce unwanted and contaminating background currents, this novel technique allows several cardiac ion channels to be studied.

The dAPC technique represents a promising new tool to study various cardiac ion channels and may also prove useful in related fields of research, e.g. in neurophysiology.

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Reduced mitochondrial efficiency: dysfunction or defence in ageing muscle?

Mitochondrial oxidative phosphorylation has been found to become less efficient with age in both mouse and human skeletal muscle. Here, David Marcinek explores mechanisms that can lead to either a protective or pathological effect of this uncoupling

David Marcinek

Mitochondria are primary sites for aerobic ATP synthesis and generation of reactive oxygen species (ROS). They also play an important role in regulating cell survival. These multiple roles of mitochondria place them at the centre of the cellular mechanisms responsible for a growing number of pathological conditions. Despite an explosion of research into mitochondrial function in ageing and diseas,e there are important issues that remain unresolved. One of these is the significance of the coupling efficiency of oxidative phosphorylation (P/O).

Reduced mitochondrial coupling in ageing tissues presents an interesting paradox. Reduced coupling has been demonstrated to reduce the generation of ROS by the mitochondria. However, uncoupling with age is also associated with impaired ATP synthesis and altered cell energetics. Therefore, certain changes associated with reduced coupling, such as reduced ATP levels, may be detrimental to cell survival, while others, like a decrease in ROS production, may be an adaptive response to cellular stress. Here I focus on mechanisms and significance of reductions in mitochondrial coupling efficiency in ageing muscle.

We have recently demonstrated significant mitochondrial uncoupling *in vivo* in aged mouse skeletal muscle (Marcinek *et al.* 2005). Using a combination of magnetic resonance and optical spectroscopy to directly measure ATP use and O_2 uptake *in vivo*, we found that mitochondria in aged mouse skeletal muscle produce on average about 50% fewer ATP molecules per O_2 molecules consumed (reduced P/O) than those in young muscle (Fig. 1). This mitochondrial uncoupling is consistent with the reduced *in vivo* phosphorylation capacity per mitochondrial volume found in the quadriceps from elderly humans (Conley *et al.* 2000). Mitochondrial ATP synthesis is coupled to oxygen consumption in the mitochondria through the membrane potential generated by proton pumping in the electron transport chain (ETC) (Fig. 2). This membrane potential provides the driving force for protons to flow back into the matrix, which drives ATP synthesis by complex V (F_1F_0 ATP synthase). Protons may also bypass the ATP synthase and leak across the inner mitochondrial membrane (IMM), short-circuiting the coupling of ATP synthesis and O_2 consumption. This leak will dissipate the membrane potential and reduce the efficiency of oxidative phosphorylation (lower P/O).

Increased proton leak is the most well accepted mechanism to explain the lower P/O values in aged muscle. This hypothesis is supported by results demonstrating increased proton leak in mitochondria isolated from aged rodent muscle (Harper *et al.* 2004). Such proton leak may occur as a result of non-specific leak across the IMM resulting from damage to membrane components in aged muscle, or the leak could be mediated through activities of specific membrane proteins, such as the uncoupling proteins (UCP). These leak pathways are not necessarily mutually exclusive, but identifying the roles of membrane damage versus UCP function may be critical to determining whether uncoupling represents mitochondrial dysfunction (damage) or a regulated cellular response to stress (UCP) in ageing muscle.

One mechanism for increased mitochondrial proton leak with age is that oxidative damage to mitochondrial proteins and lipids leads to membrane damage making the IMM more permeable to protons. The accumulation of oxidative damage to mitochondria is well documented in aging tissues and damage to membrane lipids has been shown to increase proton leak in isolated systems. Further support for a role for oxidative damage in mitochondrial uncoupling comes from transgenic mice with reduced antioxidant activities.

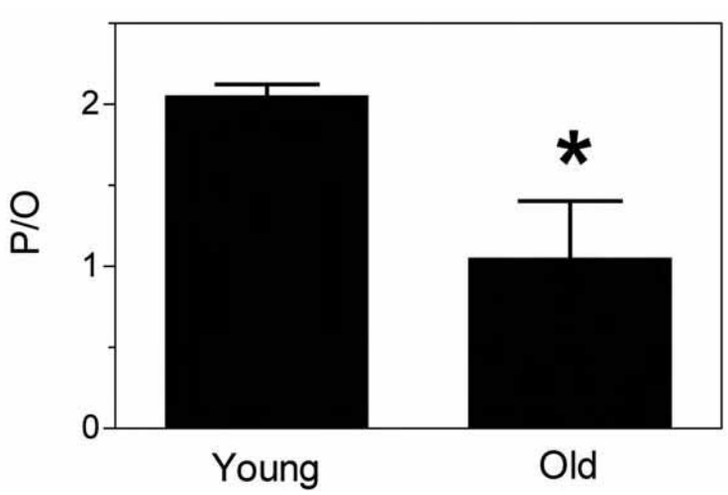

Figure 1. Severe uncoupling in aged mouse skeletal muscle. Mitochondrial O_2 consumption and ATP synthesis were determined *in vivo* in resting mouse hindlimb muscle. The ratio of ATP produced per O_2 consumed (P/O) was approximately 50% lower in the old (30-month) mouse muscle than in the young (7-month) mice (* $P < 0.05$). Data from Marcinek *et al.* (2005).

Mitochondria isolated from these mice had higher levels of oxidative damage and lower respiratory control ratios (state 3/state 4 respiration) (Williams *et al.* 1998), which is indicative of increased proton flux across the IMM.

In contrast, an increase in mitochondrial proton leak with age may be due to an upregulation of UCP activity. Increased proton leak through the UCPs would lower the membrane potential and lead to reduced ROS production by the ETC, because mitochondrial ROS production is very sensitive to changes in the resting membrane potential. This means that even a small amount of proton leak due to UCP activity could lead to large decreases in ROS production.

This idea has led to the proposal that mitochondrial uncoupling is actively regulated through UCP function as a defence against oxidative damage to mitochondria. Uncoupling by UCP3 in muscle has been found to increase in response to lipid peroxides (Echtay *et al.* 2003). Since the lipid peroxides form in the mitochondria in the presence of increased oxidative stress their role in upregulating UCP3 activity supports a feedback model where oxidative stress leads to mild uncoupling, which in turn reduces ROS production.

The oxidative damage and regulation of UCP hypotheses are not mutually exclusive. This raises the interesting possibility of different degrees of uncoupling in aging tissues – one that may be a regulated cellular defence against oxidative damage, and one that is the result of mitochondrial damage. In the first case mild uncoupling would be due to upregulation of UCP activity in response to oxidative stress. This would create a negative feedback loop by lowering the membrane potential and reducing ROS production. Speakman *et al*. (2004) found that proton leak was greater in skeletal muscle mitochondria isolated from the longest-lived mice in a population. They demonstrated that UCP3-mediated uncoupling accounted for a significant fraction of the difference between the longer- and shorter-lived individuals. This study provides indirect evidence for a protective effect of mild uncoupling.

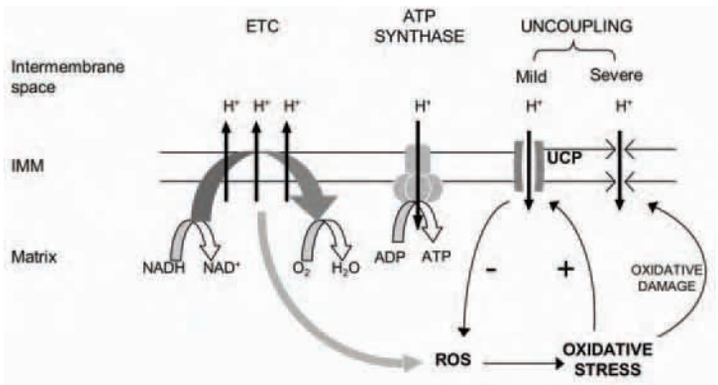

Figure 2. Schematic model of oxidative phosphorylation showing paths for uncoupling of oxidative phosphorylation. Oxygen consumption by the electron transport chain (ETC) and ATP synthesis in the mitochondria are coupled by the membrane potential created by ETC proton pumping across the inner mitochondrial membrane (IMM). The ETC also produces reactive oxygen species (ROS) that cause oxidative stress and can lead to uncoupling. In the case of mild uncoupling, oxidative stress leads to upregulation of proton leak through the uncoupling proteins (UCP). The increased leak reduces ROS generation and decreases the oxidative stress. When oxidative stress exceeds cellular defenses oxidative damage can accumulate causing membrane damage and severe uncoupling.

In contrast, the more severe uncoupling that has been found in aged mouse (Marcinek *et al.* 2005) and human (Conley *et al.* 2000) muscles *in vivo* is more likely associated with mitochondrial damage and dysfunction. The presence of mitochondrial dysfunction is indicated by reductions in the cell's energy state (ATP/ADP) and/or ATP levels that accompany the lower P/O values in both species. The change in the cellular energetics is a sign that the ability of the mitochondria to meet the energetic demand of the cell is compromised in these tissues. Because reduced ATP levels can be signal for apoptosis, the severe uncoupling may be an early step in the pathway toward tissue degeneration.

In the model presented here UCP-mediated mild uncoupling acts as a regulated, adaptive response to reduce mitochondrial oxidative stress to minimize oxidative damage. When mitochondrial oxidative stress increases with age or in disease states, eventually the level of oxidative stress exceeds the ability of the cell to counteract this stress and the result is damage to mitochondrial DNA, proteins, and lipids. This damage accumulates leading to mitochondrial dysfunction, including the severe uncoupling we have identified *in vivo* in aging skeletal muscle. The associated disruption of cellular energetics and reduced ATP levels may then push the cell toward apoptotic cell death and lead to tissue degeneration. Under this scenario, differences in UCP expression and the degree of mild uncoupling would indicate differences in defense against oxidative damage and contribute to the variation in mitochondrial dysfunction and tissue degeneration found in different tissues.

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Granny's going global...

Investigating the organisational and functional principles operating within the social brain involves establishing causative links between behaviour and multi-component neural systems. With the introduction of new techniques for monitoring brain activity, are we now advancing towards an understanding of how brain systems mediate social cognition? Alister Nicol and colleagues look at current strategies and some of the challenges lying ahead

Alister Nicol (left), Hanno Fischer, Andrew Tate and Keith Kendrick.

Progressing in our career, finding a partner, leading a social life – living in a modern society is a complicated business. It is all about 'how to play the game', which 'pack to join', whom to interact with and how, in order to succeed. We are well equipped for this task: our brains possess specialised neural systems for perception, processing, assessing and memorising the vast amount of sensory information related to individual identity, emotional state and attraction, the interpretation of which guides our social behaviour. These neural systems are not unique to us humans and have been demonstrated in many social mammals including monkeys, ungulates, and rodents (Tate *et al*. in press).

Many species use visual cues to identify one another and communicate social signals, with the face playing an important part in human and primate societies. Others, like rodents, use odour cues for individual recognition. While the sensory receptors in our eyes and noses are exquisitely sensitive in detecting and conveying visual and odour cues from other individuals to our brain, it is the brain which must decode the constant stream of information, interpret its relevant features, and memorise and recall them in a wide range of different social contexts.

So how do our brains achieve this? And how do we find out?

In humans, non-invasive techniques for monitoring brain activity such as fMRI, MEG and EEG, in the context of individuals carrying out visual or olfactory recognition tasks, have revealed the topography and global organisational aspects of the underlying brain systems. However, interactions amongst individual neurons within the neuronal networks involved have yet to be revealed.

Our current understanding of encoding strategies within such networks has been determined from the responses of individually recorded neurons. One major finding is that brains may encode complex visual stimuli, such as complete faces (e.g. Young & Yamane, 1992; Sugase *et al.* 1999) or an individual's specific odour (e.g. Kendrick *et al*. 1992), using very few neurons – 'Grandmother neurons', named after a hypothetical cell encoding Granny. However, grandmother neuron schemes (also known as 'sparse codes' or 'local encoding') are not the only strategy brains use to encode complex stimuli: for example, odours (often mixtures with hundreds of components) are globally represented across a cell population, each cell responding in its

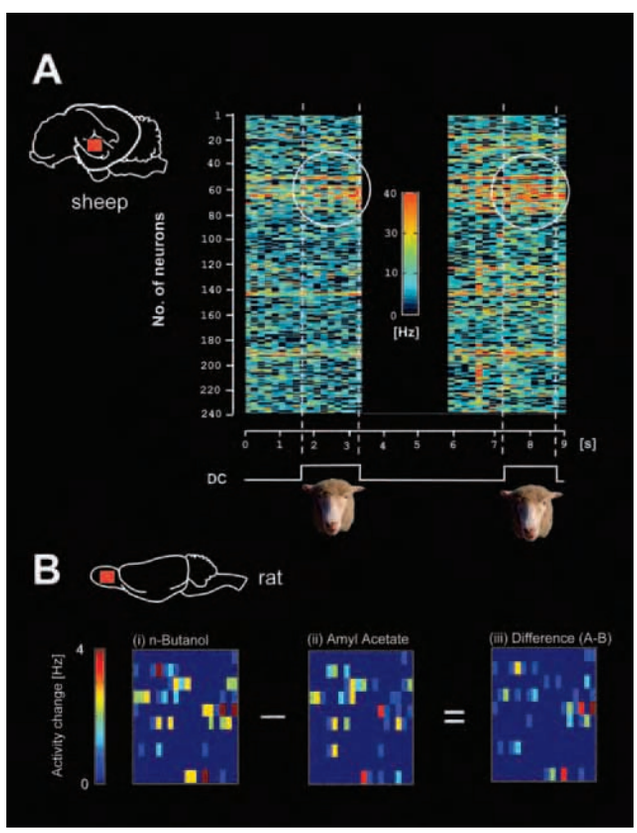


Figure 1. *A*, Multi-electrode array recordings in sheep inferior temporal cortex (red grid in insert). Simultaneous recordings were made from 238 neurons during a face recognition task. Here two presentations are made of a picture of the face of a sheep (bottom trace). Circles indicate a 'hot-spot' of activity. Spike frequencies of individual neurons (in spike sec^{-1}, [Hz]) are represented in pseudo-colour. *B*, Presentation of an odour evokes a specific pattern of activation across an array in the rat olfactory bulb. Each cell in the grid represents a change in the activity of a single neuron at a given location on odour presentation. Comparison of the array response in *ii* to that in *i* reveals that response specificity for a single odour may be supported by only a sparse sub-set of neurons (towards the red end of the spectrum in *iii*).

own way with greater or lesser reproducibility (Laurent, 2002). The neural code for Granny's face or smell, say Chanel No 5, is thereby held in the cross-cell activity patterns of the neuronal population (known as population or global encoding). Theoretically, the number of stimuli that can be encoded by an ensemble of neurons using population encoding increases exponentially with ensemble size, and so is much greater than using grandmother cells, in which the number of stimuli encoded increases only linearly with population size (Rolls *et al*. 1997).

However, the process of perception is only one side of the problem. Our current knowledge on how brains 'streamline' the influx of sensory information and extract socially important features such as identity and emotional state of individuals post-perception is still inconsistent (Calder & Young, 2005). Are high-capacity encoding schemes involving entire networks of neurons used during the initial process of streamlining, whereas grandmother schemes represent a low capacity but highly concise top-level code for memorising and recalling?

The biggest obstacle in answering these questions is that most brains consist of billions of cells (e.g. an estimated 50 billion in humans) – too many to be explored one by one. The output of any neuronal network is defined not only by the properties of its cells but even more by the interactions between those cells. Addressing network function, therefore, requires simultaneously monitoring the activities of many cells. However, most of the responsive neurons identified so far are scattered across rather large areas of the brain.

Over the last decade, many laboratories (ours included) have invested considerable time in developing techniques to monitor the activity of large ensembles of individual neurons, e.g. using real-time calcium imaging in transgenic mice. Another more widely used approach is multi-electrode array (MEA) electrophysiology (e.g. Nicolelis & Ribero, 2002). Depending on the array size (in our lab we use arrays of up to 128 electrodes), MEA techniques allow simultaneous sampling from several hundred neurons across a relatively wide area of brain tissue (several mm^2). Data capture rates are large; in our laboratory, as much as 100Mb min^{-1}. If implanted chronically, recordings can be made over a period of several months.

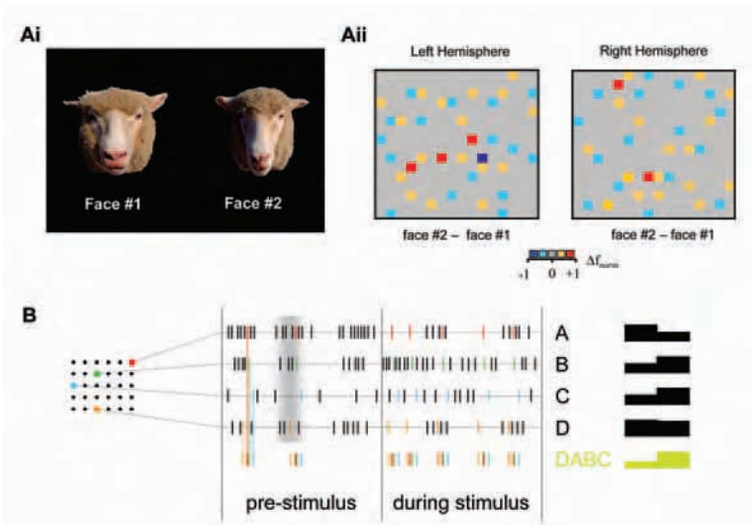


Figure 2. *A*, Changes in array responses of neurons in the sheep inferior temporal cortex related to socially relevant stimuli such as different faces (see i). (ii) In the example shown, subtraction of activity maps recorded during the presentation of two different face results in an array difference of 8%. This suggests that a successful discrimination between two faces can be achieved with very small changes in the networks. This also implies that they are capable of representing many different individual faces. Data represent normalised spike frequency changes (adapted from Tate et al., in press). *B*, Neurons across an array may be incorporated in various ways into a response. Here, spikes were sampled from 4 neurons (*A*–*D*) at four different electrodes in an array in the rat olfactory bulb. In pre-stimulus activity, neurons *A*, *B* and *D* are synchronised – they are prone to firing at approximately the same time, for example in the grey band. During odour presentation, neuron *B* becomes desynchronised from *A* and *D*. Relative firing rates pre- and during stimulus presentation (right) show neurons *B* and *C* increasing their firing rates in response to odour presentation, while neuron *A*'s activity decreases. In this respect, neuron *C* does not respond. A recurring sequence (**DABC**) incorporating spikes from all four neurons occurs more frequently during odour presentation than in pre-stimulus activity. So neuron *C*, whilst neither 'responsive' nor synchronised with any of the other neurons, is nonetheless involved in stimulus encoding.

In general, the large volume of data requires that most labs develop data processing techniques including algorithms for discriminating the activities of individual neurons (each channel of MEA data may contain the activity of several neurons) and methods for statistical analyses (e.g. Horton *et al*. 2005) in order to determine the spatial and temporal relationships between them, and so decipher the neuronal code.

Our current research focuses on (1) the contribution of individual cells in an ensemble to the overall ensemble pattern of response to defined visual stimuli such as faces, facial expressions or odours. This includes overall array differences to analyse the reliability of a representation across a recorded ensemble of neurons and the amount of overlap between individual representations; (2) activity 'hot-spots', i.e. areas of neurons in close proximity changing their activity in response to stimulus presentation (Fig. 1), and alterations in the 'temperature' and location of these areas through learning and memory; (3) correlation analyses to explore whether global stimulus properties, such as identity or expression, are reflected by the degree of synchronization between neurons; (4) stimulus encoding in spatiotemporal sequences of neuronal activity, i.e. 'patterns-within-patterns' (Fig. 2).

What do we gain?

Many current hypotheses regarding network function underlying sensory encoding can only be tested by recording the activities of many neurons simultaneously. Furthermore, computer simulations (invaluable in understanding complex systems such as brains), inevitably rely upon sufficient supporting biological data that are

(this article concludes on p. 50)

'Specific criticism'

The popular press often falls into the trap of garbling the convention for species names *i.e.* **F**orename-**s**urname (upper case, lower case) plus italic letters. The most common offences are again E(scherichia) Coli , Tyrannosaurus Rex and Homo Sapiens. But now *Physiology News* has managed it in the item reporting the Nobel Prize award to Robin Warren and Barry Marshall (**62**, 39). So, that should be *Helicobacter pylori* and not *Helicobacter Pylori* [*sic*]. Since it becomes *H Pylori* through the rest of the item, *PN* can perhaps claim consistency if not accuracy.

Another detail from *Physiology News* **62**, 3 – the explanation of the cover photos [*sic*] implies we could have expected four items of Brazilian wildlife, rather than just the one glorious iguana (and that'll be the Green iguana, *Iguana iguana*, I guess) that adorned the actual cover. Wot, no Mardi Gras images from Rio? But I eventually discovered the remaining three on the back page; very beautiful they are too. That's capybara (sing.) and capybari (pl.) for *Hydrochoerus hydrochaeris*, by the way. And is 'caimen' the plural for the caiman (*Caiman latirostris*)?

David J Miller
Institute of Biomedical and Life Sciences, University of Glasgow, UK

Cain mutiny?

When I showed Mark Cain's article (*Physiology News* **62**, 40) to my friend Batha Khani, host of the famous Indian TV show *Spat Chat*, he made several interesting suggestions to ensure high viewer ratings for physiologists. Juicy titles are necessary he felt, to draw the attention of people. A series called *Escape Artists* could feature physiologists with distaste for temperate environs, to star in episodes like *Cute Coote on high cliffs*, *Musings during freezing: little igloo on the glacier* or *Devilish dive of Neil's Donald Duck*. Debates showing Dubious Raymond pitted against Timeless Hawkins discussing the metaphysics of muscle or Denis the Menace facing Sandy Kenters to find out whether 'Heart throbs are real sparks or mere transients?' could be of interest to the addicts of reality TV. There could also be sting operations (so popular in this country) depicting physiology, philately and philandering in the recent meeting of The Society or secretly recorded rantings and chantings of drunken scientists in the wine and cheese party. Philosophical discourses, like' When does the life begin?' by the President of newly formed 'Society for Prevention of Cruelty to Stem cells' is certain to attract mature insomniacs desperately seeking an afternoon nap. Quiz contests between teams of smart, sweet and savvy purveyors of physiology, representing lifers in Liverpool or Manchester Un-united are sure to enthrall the audience. Yes Mark, you have unleashed a Cain mutiny!

J Prakasa Rao
Department of Physiology, Christian Medical College, Vellore, India.

Goal-directed limb movements

The Society for Experimental Biology Main Meeting was held at the University of Kent at Canterbury from 3–7 April. A symposium on goal-directed limb movements was organised by Tom Matheson (University of Leicester, UK) and Volker Dürr (University of Bielefeld, Germany).

Goal-directed limb movements are intrinsic to many behaviours, in animals ranging from insects to humans. Making such movements requires the solution of problems as diverse as coping with redundant degrees of freedom, planning and controlling hand or foot trajectories, integrating biomechanical properties of the limb, and compensating for postural changes that affect balance. An important goal of current neuroscience research is to develop an understanding of the sensory-motor transformations that underlie these movements. A comparative approach can reveal general principles of limb movement control, because animals as different as an octopus, a locust or a cat must all solve the same problems but their limbs and the corresponding neuronal control mechanisms have evolved independently from each other.

Our session brought together leading researchers who dealt with topics that spanned across model systems (insects, molluscs, primates, carnivores) and methods (neurophysiology, behavioural physiology, biomechanics and modelling). One recurring theme was that animals utilise many 'tricks' to simplify the control of movements. For example, Binyamin (Benny) Hochner described how, during object retrieval, the highly flexible arm of an octopus forms almost static bends that act rather like joints, and thus reduce the effective degrees of freedom of the movement. Tom Matheson described how high levels of joint stiffness can facilitate load compensation in locusts, and Volker Dürr demonstrated that aspects of stepping, searching and reaching movements in an insect can in principle be generated by a single control network. In other invited talks, Paul Gribble described how humans represent joint interaction torques, Trevor Drew provided evidence that the neural mechanisms underlying reaching in cats may have developed from those used to control aspects of locomotion, and Tamar Flash provided a wide-ranging talk on computational issues in motor control.

The talks were well attended, and feedback was uniformly very positive. A general discussion provided a valuable forum for the development of some interesting ideas, some of which were mulled over at more length during a very enjoyable evening meal attended by all of the contributors. A number of posters associated with our symposium generated considerable discussion during the main poster session.

Generous funding provided by the Company of Biologists (through the SEB), The Physiological Society, and the German Zoological Society (DZG) enabled us to support all of our invited speakers, to award travel grants to two students who presented posters and to the three selected presenters of submitted talks.

Tom Matheson
University of Leicester, UK

'Northern' Cardiovascular Research Group

The 14th annual meeting of the 'Northern' Cardiovascular Research Group was hosted by CRISTAL (the Cardiovascular Research Institute at Leeds) in the Worsley Building at the University of Leeds (pictured right) on 12 January. The meeting serves as a forum for the exchange of current research between those working in the cardiovascular field, and this year we saw researchers gathering from all over the UK – Manchester, Liverpool, Oxford, Bristol, and Glasgow.

A series of shorter talks by group members was peppered by more in-depth presentations. It was a privilege to have the British Heart Foundation's Professor Stephen Ball (*Leeds*) present the highlights of one of the most ambitious cardiovascular studies undertaken yet in the UK. The British Heart Foundation Family Heart Study was first proposed in 1996, and it was fascinating to see how it had developed in its attempt to identify genes that directly correlate with the risk of heart disease. No definitive genes have yet been identified, but areas of considerable interest are still being investigated and the study certainly showed once again that the familiar spectres of smoking and obesity reign supreme in shaping the risk of heart disease. After lunch, our guest international speaker Ernst Niggli (Bern) gave a comprehensive overview of his pioneering work on the control of calcium release from the sarcoplasmic reticulum in the cells of the cardiac ventricle. During a sparkling presentation, with the odd wave thrown in too, the latest ideas on how intracellular calcium control is regulated were delivered. Concluding the talks for the day, Barbara Casadei (Oxford) gave insight into her extensive research concerning the role of nitric oxide and the various NOS isoforms in regulating myocardial function. A topical and intriguing subject with a plethora of interactions for those interested in the regulation of excitation-contraction coupling in the heart.

The day's proceedings concluded with a poster session which gave everyone a chance to present and discuss their latest work. There was a wide diversity of research on show, and the posters provoked such intensive discussion around the room that no one seemed to notice when the food started to be served.

It was great to have such a diversity of excellence in cardiovascular research in one location for the day. Thanks are due to the British Heart Foundation, The Physiological Society and Leica for their generous sponsorship which made this meeting possible.

Matthew Lancaster
School of Sport and Exercise Science

Sarah Calaghan
Institute of Membrane and Systems Biology
University of Leeds, Leeds, UK

NC3Rs Stakeholder Meeting

The National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs) held its second Annual Stakeholder Meeting in London at the end of January. This was a chance for interested stakeholders to hear how the Centre had progressed over the previous 12 months and what plans it has for maintaining the momentum on raising the profile of the 3Rs.

The NC3Rs is an independent scientific organisation that was set up by the UK Government in 2004 to act as a catalyst for the 3Rs. It brings together academia, industry, Government, regulators, and animal welfare and protection groups with the aim of advancing the 3Rs through funding research, providing access to information and fostering collaborations.

The NC3Rs has an extensive website, which includes an Information Portal to help scientists apply the 3Rs by providing access to the most useful and relevant references. This sits alongside details about all the Centre's funding schemes and activities. An e-newsletter is issued on a monthly basis to highlight new content on the website and can be subscribed to through the site.

Lord Turnberg, Chair of the NC3Rs Board

The Stakeholder meeting was a chance for the NC3Rs staff, and the scientists that they are working with, to report on the growing list of activities that the Centre is now involved in. The NC3Rs main funding scheme awarded a total of £1million to eight projects. Successful applicants included one developing a cell-based diabetic wound bioassay and another looking at reducing animal usage by multiple antigen immunisation schedules.

There is also a small award scheme, run jointly with LASA (Laboratory Animal Science Association), which gives up to £2k for small projects, visits or training. One project already completed is the production of a DVD on refinement in primate husbandry by a group from Oxford University. Clips from the DVD are now available to download from the NC3Rs website.

The Centre takes a scientific approach to looking at where numbers of animals can be reduced and brings together groups of scientists, both from academia and industry, to think about opportunities for doing this.

One example is an initiative on experimental design which is being led by Michael Festing. A study is being carried out, in collaboration with the National Institute of Health, to assess the quality of experimental design and analysis in a sample of 300 papers reporting research involving animals. It is hoped the study will be completed by the end of the year.

The meeting also saw the inaugural 3Rs Research Prize being awarded by Lord Sainsbury. The recipient was Siouxsie Wiles of Imperial College London for her work on refining studies of gut infection in mice. She also received £10k to continue applying the 3Rs in her work.

Siouxsie Wiles receives the inaugural 3Rs Research Prize from Lord Sainsbury

Tim Watson
Communications Manager, National Centre for the Replacement, Refinement and Reduction of Animals in Research, London, UK

www.nc3rs.org.uk

Moving forward with neuromuscular transmission

Symposium speakers (left to right) : Jack McMahan (Stanford), Peter Molenaar (Leiden University Medical Centre), Hans Brenner (Basel), John Harris (Newcastle), Clarke Slater (Newcastle), Terje Lømo (Oslo), Guy Bewick (Aberdeen), Hugh Willison (Glasgow), Angela Vincent (Oxford) and Richard Ribchester (Edinburgh).

The neuromuscular junction (NMJ) provided the very first insights into synaptic transmission and continues to yield exciting new data, both as a model synaptic system and as the key to normal and dysfunctional motor control. This was evident at a one day symposium held in Newcastle on the 28 October 2005 to mark the retirement of Clarke Slater, jointly sponsored by The Physiological Society and the Institute of Neuroscience at Newcastle. Clarke has dedicated most of his research career to the study of the NMJ and the speakers who contributed to this symposium included many of his long standing collaborators. Under the title *Moving forward with neuromuscular transmission*, this was not so much a reflective day as a review of the current state of the field and a perspective of the future challenges based around two major themes of synapse formation, plasticity and degeneration at the NMJ (Bewick, Brenner, Lømo and Ribchester) and pathologies and toxins which affect the NMJ (Harris, Molenaar, Vincent and Willison).

Both formation and degeneration of synapses are known to involve extensive reciprocal interactions between motor neurone and muscle fibre to direct synaptogenesis and plasticity. The central role of agrins in this process is well established, but Hans Brenner (Basel) showed recent data that neuroregulin is dispensable and that, in some instances, the early stage formation of the post-synaptic specialisation can occur without agrin, challenging the 'neurocentric' view of NMJ formation and suggesting some autonomous organisation within the muscle fibre. The complex processes that maintain the NMJ were illustrated by Richard Ribchester (Edinburgh) who described neurodegeneration and neuromuscular synaptic protection in the Wld^s mouse mutant in which Wallerian degeneration is dramatically delayed. This has triggered a search for other genes which confer neuroprotection through the expression of mutant Wld^s protein in the motor neurone.

With respect to motor neuropathies, such as myasthenia gravis (MG), it is clear that many of these arise from autoantibodies directed against ion channels, receptors or associated membrane proteins. In this respect Peter Molenaar (Leiden) and Angela Vincent (Oxford) described how antibodies from patient groups could affect NMJ function through targeting the acetylcholine receptor (AChR) or MuSK, a tyrosine kinase receptor essential for the agrin-induced rapsyn-dependent clustering of AChR. In some instances, inhibiting AChR function by binding with low affinity acts allosterically to increase desensitisation. In contrast to AChR-related neuropathies, Hugh Willison (Glasgow) described how murine models have revealed the role of GQ1b ganglioside antibodies to induce complement-mediated NMJ degeneration. Such delineation of the antibody-dependent processes will have clear benefits for design of therapeutic interventions.

Finally, the enormous insights that can come from studies of functional anatomy were illustrated by Jack McMahan (Stanford). He showed that by using variable tilt angles and 3D reconstruction it was possible to perform high resolution electron microscopic tomographic studies of the frog NMJ with a spatial resolution of 2-3 nm. This has revealed the stereotypic orientation of docking proteins on the synaptic vesicle membrane which are associated with a highly organised arrangement of membrane-bound filamentous macromolecules found on the pre-synaptic membrane (active zone material). It has been possible to visualise the rotation of undocked vesicles in order that they become correctly orientated to the orderly array of macromolecules on the synapse. This arrangement helps maintain the vesicles and calcium channels at precise distances and, thereby, plays a major role in the vesicle fusion process.

Despite the great advances that have taken place during Clarke's career it is clear that the NMJ has not yet given up all its secrets and will continue, in the late Sir Bernard Katz's words to be 'an experimentally favourable object whose study could throw considerable light on synaptic mechanisms elsewhere'.

Colin Ingram
Director, Institute of Neuroscience, Newcastle University, UK

Richard Ribchester
Centre for Neuroscience Research, University of Edinburgh, UK

Experimental Physiology
Translation & Integration

Introducing Editors appointed in 2006

Margaret Brown

Maggie is a Reader in Cardiovascular Physiology in the School of Sport and Exercise Sciences at the University of Birmingham, where her current research interests lie in the mechanisms of vascular and microvascular remodelling in skeletal and cardiac muscle, from the molecular basis to integrated physiology and therapeutic application. The role of exercise as a modality for manipulation of blood vessel function and growth is particularly pertinent in cardiovascular and ischaemic diseases, involving studies of patient cohorts undertaking training programmes.

Jim Deuchars

Jim is Professor of Systems Neuroscience at the University of Leeds. His current research interests focus on the properties of neurons and circuits participating in control of autonomic functions.

Stuart Egginton

Stuart is a Reader in Physiology in the Centre for Cardiovascular Sciences at the University of Birmingham. Born in the North of England, he has appreciated the opportunity for travel associated with a career in science: a BSc in zoology from the University of Wales (Bangor), then a PhD in physiology from the University of St Andrews in Scotland (working with Ian Johnston), followed by a personal Fellowship for post-doctoral studies at the University of Maine in the USA (in the lab of Bruce Sidell), before returning to the UK for a post-doc at Birmingham (with Olga Hudlicka), where he has remained. Appointments in Austria and New Zealand have further broadened his scientific and geographical horizons.

Stuart has two main areas of research interest, with a degree of overlap that has varied with time. The first is how remodelling of the microcirculation is matched with the functional demands of tissue, mainly in skeletal muscle. The second involves cardiovascular control, largely concerned with the dysfunction associated with hypothermia (see *Physiology News* **60**, 12).

New members of the *Experimental Physiology* Editorial Board, from the top: Margaret Brown, Jim Deuchars, Stuart Egginton, Simon Langley-Evans and Paolo Madeddu.

He has served on the Council of the British Microcirculation Society and the Society for Experimental Biology, and recently retired as Convener of the Comparative Physiology SIG.

Simon Langley-Evans

Simon is Chair in Human Nutrition at the University of Nottingham, UK. His research is focused on the developmental origins of health and disease. Using animal models in which the maternal diet is altered during pregnancy, he is studying the long-term changes in renal and vascular physiology of the resulting offspring and the molecular basis of developmental programming.

Paolo Maddedu

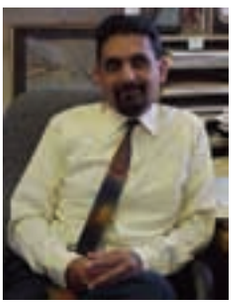
Paolo is cardiologist and chair of Experimental Cardiovascular Medicine at the Bristol Heart Institute, University of Bristol. His research, funded by charities and the European Community, focuses on therapeutic angiogenesis using growth factors and stem cells for the cure of ischaemic complications with special emphasis on diabetes. The group leaded by Prof. Madeddu has discovered the angiogenic property of human tissue kallikrein, nerve growth factor, and PAR2.

Simon Malpas

Simon is an Associate Professor in the Department of Physiology and the Bioengineering Institute at the University of Auckland, New Zealand. His primary research interest lies in understanding the role of the sympathetic nervous system in the development of hypertension. His research interests include neural control of the circulation, medical device development and telemetry.

Kaushik Patel

Kaushik is a Professor in the Department of Cellular and Integrative Physiology at the University of Nebraska Medical Center in Omaha.



New members of the *Experimental Physiology* Editorial Board, from the top: Simon Malpas, Kaushik Patel, Michael Shattock, Javier Stern and Michael White.

His general research interest is in neural control of the circulation in health and diseases such as heart failure, diabetes and hypertension. His current focus is on the role of the paraventricular nucleus of the hypothalamus in the control of fluid balance.

Michael Shattock

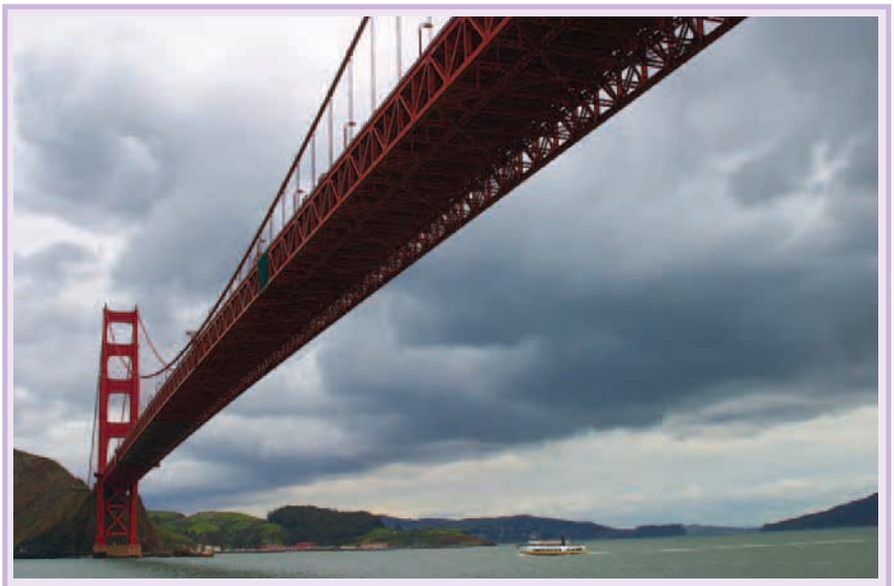
Michael is Professor of Cellular Cardiology at King's College London. He runs The *Cardiac Physiology Research Group* within the Cardiovascular Division of King's College London. The Group's general interests lie in studies of the regulation and function of ion translocating proteins in the cardiac myocyte in health and disease. The group exploits a range of models and techniques including molecular and protein based studies, single cell electrophysiology, cell cultures, isolated muscles and isolated hearts. Current interests of the group include (i) the regulation of Na/K ATPase by the accessory protein phospholemman, (ii) the role of T-type Ca channels in cell growth and proliferation, (iii) signalling in ischemic preconditioning in adults and neonates and (iv) regulation of signalling and ion translocating by thiol modification and oxidant stress.

Javier Stern

Javier is an Associate Professor in the Department of Psychiatry at the University of Cincinnati, USA. His general research interestx relate to understanding the cellular mechanisms controlling neuronal excitability, synaptic connectivity and plasticity in central neuronal circuits involved in autonomic and neuroendocrine control, including ion channel modulation of electrical activity of hypothalamic neurones, neuronal structural and functional plasticity in health (exercise, lactation) and disease (hypertension, heart failure, diabetes) conditions.

Michael White

As an undergraduate Mike read physiology at the University of Leeds and then worked in the MRC Environmental Physiology Unit in London before completing a PhD at the University of Nottingham. In 1986 he moved to Birmingham and the then newly formed School of Sport and Exercise Sciences, where he has remained ever since. Now Reader in Exercise Physiology he has worked on human thermoregulatory and exercise physiology, the effects of disuse and ageing on human muscle function and human cardiovascular control during exercise in health and disease.



The Editorial Board of Experimental Physiology now holds one of its two meetings each year in the USA to coincide with the FASEB Experimental Biology Meeting and to facilitate attendance by the increasing number of overseas Editors.

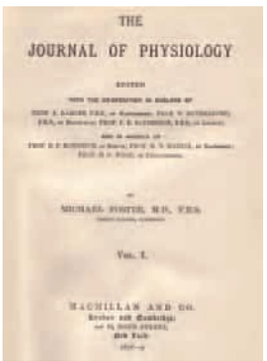
A good percentage of the Editorial Board, including five new Editors, were able to attend the meeting held this year on 3 April in San Francisco (*photo by Prem Kumar*).

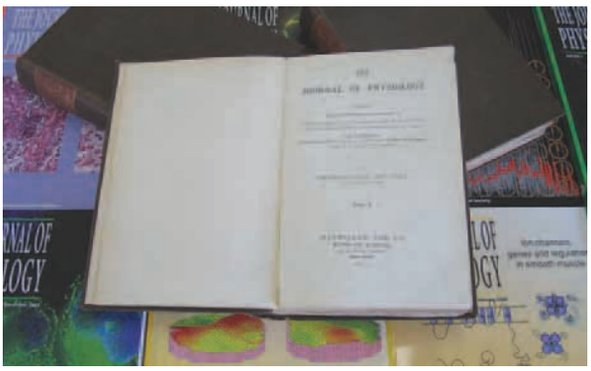
A century (and more) of physiology now online

Early in May the complete scanned archive of *The Journal of Physiology* finally went live on PubMed Central (PMC).* The scanning and checking of around 15,000 articles (no-one has actually counted them) published between 1878 and 1997 has taken longer than expected, but the results are impressive. Within a few months the remainder of the archive, from 1998 to 2005, will also appear on PMC. At that point the only content not present on the PMC site will be the most recent year's issues which are available to subscribers on HighWire and Synergy.

The Wellcome Trust has provided most of the funding for the archive project, part of a joint initiative with the Joint Information Systems Committee to digitise the archives of historically important medical journals. A launch party to celebrate the publication of the archive was held on 11 May at the Wellcome headquarters in London (pictured on p. 51), attended by various Officers of The Society and staff from The Society's Publications Office in Cambridge.

Aside from the great classic papers familiar to every student, there are many curiosities from the past to discover in the archive. Try **54**, 244–247 or **57**, 175–180 for a view of the questions and technological difficulties that troubled physiologists early last century. While many of the titles do not draw the casual reader in, some are intriguing. An article on *The phosphurus distribution of resting fly muscle* (**80**, 231–237) had me wondering how many flies were required for the experiments ('enough') and how they were caught ('easily'; the flies were reared in a cage which was then darkened while a beaker illuminated at the back end was held at the cage opening). *Observations on the composition of alveolar air on Everest, 1933* by Raymond Greene (**82**, 481–485) is a fascinating account of physiology in the extremes, to be contrasted with the report in the last





Then and now – *The Journal of Physiology* in 1878 and 2006 (above) and the development of *Experimental Physiology* over the years (left).

issue of *Physiology News* by John Coote and Thelma Lovick (**62**, 16).

The scanned archive is by title, author, institution, references and abstract keywords, and a PDF of the full paper can be downloaded. The front and back matter – editorial board lists, indexes, notices and advertisements – are available through links at the foot of each issue's contents list and are interesting to sample. In 1934 CF Palmer (London) Ltd, Makers of Physiological and other Scientific Apparatus, were selling their Rubber Bellows Respiration Unit for £14 15s, quite a price in today's money.

A little earlier in the year the complete scanned archive of *Experimental Physiology*, formerly *The Quarterly Journal of Experimental Physiology,* was published on the HighWire site.† This project was funded by The Society and organised by HighWire Press.

Like the *J Physiol* archive on PubMed Central, the *Experimental Physiology* archive is free to all readers and consists of searchable PDF files of all papers back to 1908. There are still some glitches to iron out on the site. The print archive we obtained for scanning did not include information about months of publication, and hence the repeated months in many of the early years on the archive page. (If anyone knows where there is a collection containing the first 25 issues of the *Quarterly Journal of Experimental Physiology* (1908–1936) I would like to hear of it so that we can update the contents lists.)

Experimental Physiology contains its share of classic papers. John Coote's Top Ten papers list begins with (1) Sherrington C S (1908). Some comparisons between reflex inhibition and reflex excitation. *Q J Exp Physiol* **1**, 67–78; (2) Barrington F J F (1925). The effect of lesions of the hind-brain and mid-brain on micturition in the cat. *Q J Exp Physiol* **15**, 81–102. (3) Liddell E G T (1953) (Sharpey-Schafer lecture). The brain and muscle management. *Q J Exp Physiol* **38**, 125–137.

But there is also plenty to interest the more generalist reader within the lists for each year. In a paper on *The action of tobacco smoke, with special reference to arterial pressure and degeneration* by W Emerson Lee (**1**, 335–358), it is noted, more than half a century before the dangers of smoking were taken seriously, that 'arterial disease may result from prolonged tobacco smoking'. A review by McCance & Widdowson on *The chemical structure of the body* published in 1956 (**41**, 1–17), based on the Scharpey-Schafer Memorial Lecture, provides, as well as a detailed account of nutritional studies up to that point, an insight into the prejudices and perceptions of the time.

Both archives offer a vast resource for physiologists and all students of life science. Every week I get several requests for copies of articles from the journals that up until now have only been available in departmental libraries. It will be a pleasure to be able to refer readers to the archive sites.

Carol Huxley

* http://www.pubmedcentral.gov/tocrender.fcgi?journal=236&action=archive
† http://ep.physoc.org/contents-by-date

Babies and the bench

In the last issue, Patricia de Winter questioned why there are so few senior women scientists. In this issue Dola Akanmu, a mother–of–two who has just obtained her PhD, examines the challenges that face women who have children and wish to continue in research

Bench work and babies is easy. In fact, any work and babies is easy providing suitable childcare is in place and you have a great boss who understands the practical problems of having to literally drop everything if your child becomes ill. This statement is, of course, dependent on many other factors: the type of experiments you do and whether your work schedule is flexible, for example. Some women have undertaken flexible working arrangements that suit all parties concerned, such as working from home 1 or 2 days a week or doing 4 days on, 4 days off (as agreed by one employer). Mutually-agreed working arrangements allow you to be more focused, which is particularly important as careful planning of experiments is essential when time is at a premium.

Another factor to take into consideration is childcare, which can be a big emotional change for both child and parent. If care provided by a relative is not feasible, then finding a suitable au pair, childminder or nursery place may offer various benefits at different stages of the child's life. Some employers have recognised that in-house nurseries offer particular benefits as the child is then on site should anything untoward occur. However, if you have to commute to work you may not favour the idea of travelling during rush hour, with a pushchair, baby bags, nappies and bottles in tow.

Dola Akanmu – working in research whilst bringing up two young children can be done – it just requires organisation, determination and a sympathetic employer.

The cost of childcare is an important consideration as a full-time place can be around £1,000 per month for the under 2s, depending on where you live. In most cases this represents a large proportion of one's salary. To offset these exorbitant childcare costs the Government has provided some incentives to encourage women to return to work. Family tax credits are based on the combined salary of the parents – which can be helpful if you fall within the required income bracket. This can reduce childcare fees by up to 70% for the lower income bracket. In reality, a significant reduction is only achieved providing your joint income is well below £40k.

When your child reaches the age of 3, up to age 5, they will be entitled to a nursery voucher which is approximately £400 per term. This is most welcome particularly as the paperwork is undertaken by the childcare provider. The most recent voucher scheme works through your employer in combination with the Imagine Childcare Co-operative. Basically the employee can exchange or 'sacrifice' their gross income for childcare vouchers, and as this is deducted from the gross salary, less income tax and national insurance is payable. The maximum you can sacrifice is £50 per week or £217 per month. Providing the scheme is open to the employers of both parents, they can both claim, but there are no extra benefits if you have more than one child in childcare. You can check whether your employers have signed up at www.childcarevouchers.coop.

Achieving a good work–life balance is a constant juggling act. Rushing away from work to collect your child means that you do miss out on the social aspects of work: drinks and seminars, which are very useful for generating ideas, networking and catching up with any other business. Organising your attendance at such an event involves careful advanced planning and hence requires having adequate notice. Nevertheless working full- or part-time in research whilst bringing up young children can be done – it just requires organisation, determination, and a sympathetic employer.

Dola Akanmu
King's College London, UK

The Society's journal archives

The Journal of Physiology **archive from 1878 to 1997 is now freely available online at:** http://www.pubmedcentral.gov/tocrender.fcgi?journal=236&action=archive

and *Experimental Physiology* archive from 1908 to 2004 at:
http://ep.physoc.org/contents-by-date.0.shtml

See also A century (and more) of physiology now online (p. 40) and images from the Wellcome Trust launch party to celebrate the publication of *The Journal of Physiology* archive (p. 51)

FRS for *Experimental Physiology* Consultant Editor

Peter Hunter (right), Professor of Engineering Science and Director of the Bioengineering Institute at the University of Auckland has been made a Fellow of the Royal Society.

Peter pioneered modelling the human body using specially developed algorithms plus methods that incorporate detailed anatomical and microstructural measurements and material properties into continuum models, most notably of the heart.

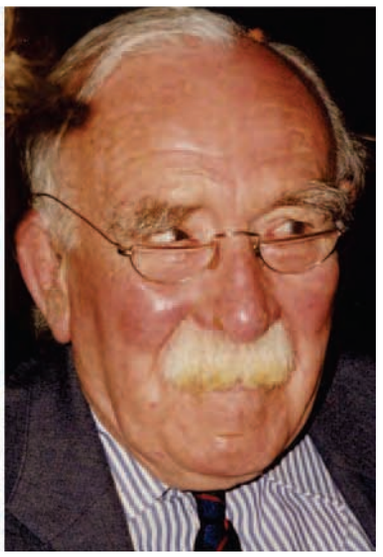
Henry Barcroft

To continue our occasional series of Memorable Members, Ian Roddie praises the formidable intellect and bonhomie of a much-loved Honorary Member

Henry Barcroft (1904–1998) was the son of a famous father, Joseph Barcroft, one-time Professor of Physiology at Cambridge. Henry qualified at Cambridge with a double first in physiology and worked at UCL with Lovatt Evans before moving to the chairs of physiology in Belfast (1935–1948) and St Thomas's in London (1948–1971). His best known work was on nervous control of human blood vessels and for this he was elected FRS in 1953 and an Honorary Member of The Society in 1974.

One of his most important and endearing qualities was his ability to bring out aptitudes and enthusiasms in the people with whom he worked. Thus he catalysed the conversion of many young graduates into professional physiologists. John McMichael, one time Professor of Medicine at the Royal Postgraduate Medical School at Hammersmith, put it like this – '*He is always surrounded by enthusiastic young men to whom he gives guidance and inspiration to a marked degree. Completely unselfish himself, he gives them every opportunity to develop their talents'*. Sir Henry Dale, the famous Nobel Laureate, put it another way when he said – *'He has given abundant evidence of his power of awakening in others an interest and enthusiasm comparable to his own'*.

Henry was a kind man – he could find a good word to say about almost anyone and character assassination was totally foreign to his nature. Nevertheless, he was a shrewd judge of character and the strength of a scientific argument. When flawed propositions were put to him by enthusiastic juniors, he handled them gently and never crushed or humiliated. He would listen attentively but then ask for the proposition to be explained again more slowly so that his 'aging brain' could



understand it fully. It was when the young enthusiast was explaining his proposition for the third or perhaps fourth time, with perhaps some exasperation, that the flaws in the proposition would become self-evident, as would the need for revision. Thus it was possible for the proponent to withdraw with dignity and self-esteem intact to think the proposition through again. Henry would encourage this and say that he looked forward to hearing the outcome.

Henry's courtesy and bonhomie made him a much loved member of The Society, but to some extent masked his formidable intellect. The other-worldliness of his outward demeanour tended to obscure a tough inner resolve to make the best of his opportunities in the real world. In making decisions, he could be quite ruthless and unswerving in his determination to do what he considered to be the right thing, regardless of the consequences. Once his mind latched onto a problem, e.g. the mechanism of functional hyperaemia, he would pursue it relentlessly with a tenacity that was almost obsessional. He had an excellent memory for scientific, but (according to his wife) not domestic, detail. He stored in his mind a huge collection of snippets of scientific knowledge that would surface when needed to interpret new data.

Henry was fortunate in being born into a stable and loving family and this good fortune was to stay with him throughout his life. He was devoted to his family – his wife, children and grandchildren – and he always spoke of them with the greatest affection. He was lucky, especially in this day and age, that this affection was returned and they gave him their love and support right to the end.

Ian C Roddie

See also Memorable Member – G L Brown (*Physiology News* **62**, 34).

Mistaken identity!

As many Members know, The Society was founded in 1876 as a Dining Club. In 1941, at a Society meeting in Cambridge, Charles Sherrington, one of the Founding Members, reminisced about those early days. Luckily a verbatim report is included in the short account of The Society's second 50 years produced in 1976 to mark The Society's Centenary (Bynum, 1976). Sherrington recalled that J S Burdon Sanderson, another Founding Member and first Waynefleet Professor in Oxford, was notoriously absent minded. He went on to say that he and eight or nine others were upstairs in the study at Burdon Sanderson's home when Gaskell embarked on a long dissertation on his current theories. After a time the dinner bell rang but Gaskell continued the argument; in the end Lady Sanderson called upstairs that dinner was served. Gaskell went downstairs followed by Sanderson and the rest. The dining room door was open and Lady Sanderson already seated at the table. Gaskell, still propounding his views, went to the head of the table, seated Sanderson on his right and began to carve; suddenly he looked up at his hostess, and said, 'Pardon me, I thought I was in my own house'. Sherrington added 'That made two absent-minded Members at the same time.'

Ann Silver

Reference

Bynum WF (1976). A Short History of the Physiological Society 1926–1976. *J Physiol* **263**, 23–72.

Send us your recollections of past Members of The Society for inclusion in our Memorable Members series. Contributions to lrimmer@physoc.org

Parliamentary and Scientific Committee

The January meeting of the Parliamentary and Scientific Committee at Portcullis House, Westminster, covered the topic *Hospitals of the future*.

In his introduction, Sir Richard Sykes, Rector of Imperial College London, postulated that hospitals of the future will revolutionise the way in which hospital care is delivered thanks to the impact of new technologies together with major demographic and sociological change. He suggested that new healthcare technologies, including robotic surgery, wearable and implantable monitors exploiting wireless communication and new IT systems will change both the environment and the staff base required. Diagnosis and treatment would be more in the hands of specialised technologists rather than general physicians. Remote monitoring would greatly change the location of patient care towards a home base and hospitals would retain more specialist functions.

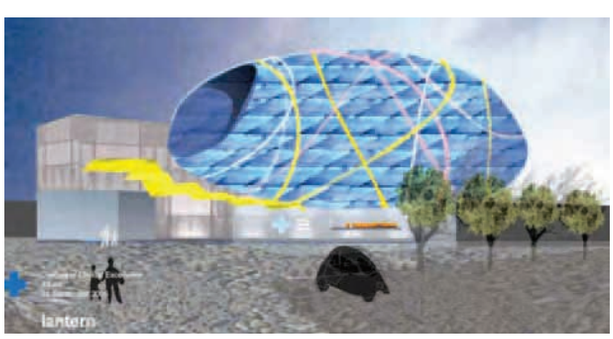
Richard Kitney, Professor of Bioengineering at Imperial College, described the development of an England-wide medical database and how the local intranet and internet together provided an integrated system for the storage and analysis of patient data and the potential for remote diagnosis and even robot-based treatment. He commented that this had been greatly enhanced by the development of generic components for data storage and processing in many spheres of life, which was rapidly bringing down costs and putting enormous power and access to data into wirelessly connected hand-held devices. (Maybe we will even be able to keep our mobiles switched on in hospitals).

Susan Grant (Projects Director, Atkins Design and Engineering Solutions, whom we thank for the illustrations of future hospitals), an architect who specialises in hospitals, carried on this theme, showing how hospitals in many parts of the world were already incorporating new technologies in ways that were changing their architecture, allowing creative approaches to building, particularly pre-fabrication and the concept of the disposable or upgradable ward unit (the ubiquitous term 'pod' was used both for room units and mobile surgical theatres) to respond to changing technology and the challenges presented to hygiene by the threat of pandemics.

Sir Ara Darzi of the Division of Surgery at the, by now remarkably well represented, Imperial College, discussed the impact of changing technology on the culture of the patient-professional interaction and how alternative evaluations of clinical success by either prevention or cure could have a major influence. He suggeted that the private sector would deal with minor and elective treatments while the NHS would concentrate on major treatments in specialist centres. He felt that the concept of the 'local general hospital' had had its day. In the later discussion it was felt that selling this idea to the public was a major factor that would need to be carefully argued, given the attachments of both local populations and clinical staff to 'their' hospitals. Ms Grant indeed felt that eliminating the term 'hospital' would allow more constructive discussion, though this did have a touch of the Orwellian about it.

There was a frisson from the left-leaning politicians present when Ara Darzi mooted that patients' perceptions tended to favour the private sector in certain contexts. Apart from this there was remarkably little political controversy, given the undoubtedly enormous costs of the new technologies involved and the consequences for the individual of insurance companies knowing predictors of their health status, though data-security did emerge as a major concern.

For teachers of physiology, the implications are interesting. The physicians and surgeons of the future will undoubtedly have to adapt to more specialised roles. General practitioners and others involved in community care will play a greater role in technology-based diagnosis and treatment, as robotics and IT rolls this away from the hospital. Their training will need to fit them for this, perhaps by emphasising the current trend towards learning how to learn rather than acquiring information. They might also need a harder edge to their scientific and technological knowledge. There will undoubtedly also be a need for high-grade technologists, graduates with an undertanding of human biology and the flexibility to adapt to changing technologies. Our teaching of science and medicine will need to adapt.



Ian McGrath

New Chief Executive

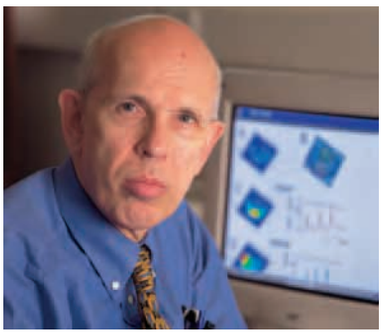
Michael Collis has been appointed as The Society's new Chief Executive. He will be responsible for helping to shape and deliver the strategic vision of The Society, interacting closely with the Trustees and Executive Committee and maintaining well-established links with other learned societies. We have been fortunate to have recruited an established scientist with a long-standing interest in physiology and a broad range of experience in academia and industry.

Michael has spent the majority of his research career in industry, where he held senior research management positions at Wyeth, ICI and Pfizer and advanced 16 novel drug candidates into clinical development. As lead of the Academic Liaison and Collaboration group for Pfizer, Michael established numerous links with academic researchers and learned societies. He has published extensively, particularly on the role of purinergic receptors in the cardiovascular system and has served on the Editorial Boards of *Hypertension* and the *British Journal of Pharmacology*. Michael is a strong believer in the importance of integrative physiology, and is currently a member of the BBSRC Studentship and Fellowships Committee, MRC Physiological Systems and Clinical Sciences Board and the RAE (2008) Pre-clinical and Human Biological Sciences Panel.

Michael Collis took up office in early May and is based at The Society's London Office.

New President

The Physiological Society is delighted to announce the election of Ole Petersen, FRS as The Society's new President. Ole is currently George Holt Professor of Physiology and MRC Professor at the University of Liverpool and holds honorary executive positions as Vice-President of the Royal Society, Secretary General of the International Union of Physiological Sciences (IUPS) and Chair of the Physiological



New Society President Ole Petersen

Reviews European Editorial Committee. Ole received his MB ChB (1969) and MD (1972) from the University of Copenhagen and was appointed in 1975 as Symers Professor of Physiology and Head of the Department of Physiology at the University of Dundee. He was elected as a Fellow of the Academy of Medical Sciences (FMedSci) in 1998, The Royal Society in 2000, the Royal College of Physicians London (FRCP) in 2001 and has been the recipient of numerous other prestigious awards and lectures. Ole Petersen's current MRC programme grant focuses on pancreatic acinar physiology and pathophysiology, with a particular interest in the regulation of ion channels and Ca^{2+} signalling in secretory cells. He has published extensively in the field of physiology and has been a long-standing supporter of the discipline. Ole played key roles as a member of The Society's Council (formerly Committee) and as its International Secretary from 1992–1998. He will take up his post in July 2006.

Ole writes: '*I look forward to working with the Executive Committee and Council to further enhance the effectiveness and international reputation of The Physiological Society, which I have always regarded as my principal Society*.

From my current work as European Editor of Physiological Reviews *I know that physiology can have a very high impact and I therefore believe that the future is bright for our science as well as our Society*.'

Alan North

Council elected Alan North, FRS as President of The Physiological Society in 2003 and he will be stepping down at our AGM at University College London in July 2006. I recall Alan's comments when he took over as President from Colin Blakemore, FRS at the AGM in the University of Manchester - Alan stated that he hoped to play a key role in the promotion of the discipline of physiology and The Society, especially in an era when traditional departments of physiology were now scarce. Moreover, he felt that The Society and its President needed to be pro-active in promoting the awareness and understanding of physiology in academia, government, industry, and society at large, especially young people who would become the physiologists of tomorrow.

On behalf of the Executive Committee, Council and the membership, I would like to thank Alan for his invaluable advice during the past 3 years. As Chair of our Council meetings, Alan played a key role in launching annual November breakout groups which not only reviewed The Society's ongoing activities but also identified strategy for the coming year. In addition to representing The Society in the UK and abroad, Alan together with our International

Secretary David Eisner, was instrumental in securing the International Union of Physiological Sciences (IUPS) meeting for the UK in 2013.

Alan has certainly raised the profile of physiology and The Society. His wide range of physiological research interests and extensive international experience, underpinned by the respect of scientific community for his research, have ensured that physiology remains at the forefront.

Apart from his role as President of *The Physiological Society*, Alan is currently Vice President and Dean of the Faculty of Life Sciences at the University of Manchester and Chair of the Pre-clinical and Human Biological Sciences RAE 2008 panel. I have valued working closely with Alan and thank him for his continued support and guidance in the recent appointment of The Society's new Chief Executive, Michael Collis.

Giovanni Mann

BIOSCIENCES FEDERATION

Richard Dyer

Much of the work of The Biosciences Federation (BSF) is conducted through its standing committees. Currently these cover education, animal science, environmental sustainability and Europe. One of their responsibilities is to scan the horizon to look for issues that may impact upon the biosciences because of new policies and legislation. Often these changes will effect more than those of us with careers in biology – and this is especially true with developments on a European scale.

In my view we failed to realise in advance the full impact that the Fixed Term Directive would have on the employment of young people in our laboratories. You will know that today a first postdoctoral position can be regarded as 'training' but that a second 3 year postdoctoral position in the same laboratory usually makes the individual permanent. That is, he or she has tenure and will have to be made redundant at the end of the 6 years. As a consequence, and even though the second 'postdoc' is often more productive than the first one, laboratory heads frequently now undertake a cost benefit analysis when thinking about keeping a 'postdoc' for a second term. Whilst the cost of redundancy varies from place to place, legislation usually requires that there is an agreed process for the redundancy procedure. All of this is an additional burden for science to carry and was not adequately foreseen and certainly not discussed forcibly with our policy makers when there was a window for influencing the legislation. Of course, I don't for a moment think that it was at all appropriate in the past to have scientists on rolling 3 year contracts for decades, and am glad that those days have gone. However, with the right arguments made at the right time it might have been possible to have obtained agreement that 'training' for 'postdocs' could last for up to 6 years. Making such arguments is the role of the BSF.

There is good news currently coming from Brussels. I am sure now that there will be a European Research Council (ERC) and that it will have a budget of at least €1bn per annum. This will come from the FP 7 budget of €54bn for 7 years. You may be interested to know that this budget is 40% higher than for FP 6.

I write that this is 'good news' because I think it highly desirable that a UK bioscientist can have the opportunity to apply for response mode funding with a colleague from the mainland without having to go through the contortions that have been necessary in the past. On this occasion, I think that the European Commission (EC) has been on the side of the angels! They have resisted all attempts by national or special interest groups to dominate the ERC. As an example, the EC forbad the ERC Council from having 25 members! Any other number was allowed but not one per state. There will be no *juste retour*: there was a time when ERC was going to mean European Research Competition.

All of this is very positive news – but there are some formidable problems ahead. First, think about what science means in a European context. It covers 25 states and includes the humanities and social sciences. Second, think about the budget. €1bn is roughly the same as the budget that our new Medical Research Council can anticipate. Clearly, it is inconceivable that scientists from 25 countries can have open access to the new ERC. The organisation would sink without trace beneath the many thousands of applications, and even if these could be processed, with a high standard of peer review, the success rate would be so low that the ERC would be discredited.

The solution to this significant problem is being sought and part of the solution may come from reserving funds for 'young investigators'. There is currently a suggestion that 30% of the budget will be made available only to those just starting their careers. But this will merely create another problem. 'Young' means very different things in different countries. If it is defined as 6 years 'postdoc' then it means 30 in the UK but nearly 40 in quite a few other EC countries.

Whatever is decided, it seems inevitable to me that access to the ERC will have to be restricted somehow. The BSF, through its European Liaison Group, will be closely watching how this develops and we will respond on your behalf when an appropriate occasion arises.

Richard Dyer
Chief Executive, Biosciences Federation
(http://www.bsf.ac.uk)

Bridget Lumb

Bridget Lumb was elected as Meetings Secretary of The Physiological Society in 2002 and was the first female member of the Executive Committee under The Society's new governance. Bridget has been extremely energetic in devising and implementing the new format for our Scientific Meetings. We now host one Main Meeting and 4–5 Focused Meetings each year. The intention of the Meetings Committee, chaired by Bridget, was to provide an improved international forum for the dissemination of scientific findings and, in doing so, to raise the profile of The Society. As you will know, the restructuring of our Meetings has led to a pre-meeting vetting of abstracts and replaced the previous system of voting at Scientific Meetings. Amongst the highlights of Bridget's tenure was her key involvement in initiating the discussions that resulted in The Society hosting the first joint meeting with the Federation of European Physiological Societies (FEPS) at the University of Bristol in July 2005. At the Bristol Meeting, Lord Sainsbury of Turville (Parliamentary Under-Secretary of State for Science and Innovation), met with the Executive and spent an afternoon discussing science with poster presenters. Bridget also introduced the novel concept of a Public Lecture into the programme, and this practice has now been adopted for our future Main Meetings.

Bridget was the first Meetings Secretary to run a Meeting with no abstracts in Seville in 2003. Bridget excelled in presenting the minutes of our Scientific Meetings at Society dinners, and I recall an extremely entertaining after-dinner speech in the University of Cork, where a number of Members and guests found it almost impossible to suppress their laughter...was this due only to a loss of audio support or the fire alarm? Bridget will be stepping down as Meetings Secretary in July 2006, and on behalf of the Executive, Council and membership, I would like to express our thanks for her invaluable contributions to The Society. Although we will miss Bridget's humour and friendship, I know that she will retain a close association with The Society. Prem Kumar has been nominated by Council as the Meetings Secretary Elect and is currently liaising closely with Bridget to plan meetings for 2007–2008.

Giovanni Mann

Oi, ref!

On the whole, scientists are a reasonably polite bunch. Of course, there are exceptions but, in general, a fairly high standard of courtesy is the norm. So, for example, in the course of the average 'free communication' session at a conference – even when the content of a paper leaves something to be desired – overt rudeness or hostility is pretty rare. Unless, that is, you are disastrously unlucky, or are presenting your work to the British Pharmacological Society. As a PhD student, I used to view the 5 minute question session with great trepidation, not to say dread. The weaknesses of my presentation, obvious even to myself, were certain to induce a verbal firestorm. But pretty soon I realised that the worse outcome was likely to be a complete lack of questions, leaving the hapless speaker – me – in a state of suspended animation and creating an all-round feeling of anticlimax. Questions from the audience were welcome, and the vast majority of comments – even those hinting at shortcomings in the work – were almost invariably non-adversarial.

So at times, often having just presented a talk myself or otherwise sitting in the audience, I find myself wondering who and where are the individuals responsible for refereeing one's *written* work? The ones who produce those comments that indicate everything from not actually having read what you've written, wilful misunderstanding, strong personal bias through to sheer spite and nastiness? Who are those guys?

Are they the same folk who asked you the questions when you presented the work orally a few months ago? Or are they hidden in the anonymous sea of silent faces, keeping quiet for the time being but dreaming up something nasty for possible future use? Or are they somewhere else altogether, more interested in what's going on in another lecture theatre, or in the bar?

Obviously the content of a full published paper is considerably more important than that of an oral communication. The latter is often a form of a 'try-out' of novel data, and probably isn't going to get published anywhere prominent, except maybe in abstract form. A full published paper, on the other hand, represents (or at least should represent) the final considered article, as near perfect as is practicable. So it's only fair that it should be subject to greater rigour in the review process. But why does this process have to be so often accompanied by verbal heavy artillery? And as for the treatment of grant proposals…don't even go there. The phrase 'give 'em both barrels' comes to mind.

I'm sure everyone reading this (apart from those elite scientific beings who are so brilliant they are never on the sharp end of all this) will have their own examples of referees' comments indicating ignorance, prejudice or just downright disdain, so I won't bore you with any of my personal collection. But why do the reviewers of papers and grants feel moved to provide this kind of comment and criticism?

The most obvious answer (apart from the criticism being well-deserved) is that the refereeing of papers and grants is still predominantly anonymous. The pros and cons of anonymous refereeing have been broached many times in recent years, including in these pages, and I do not propose to drag the subject up again. However, I still feel personally that an 'open' system of refereeing would encourage reviewers to be more accurate and objective – and probably more helpful and courteous.

Another factor in the process of refereeing is that it is a pretty thankless task. It seems to me that this is fundamentally wrong, given the influence that referees exert over the career prospects of the scientist. Refereeing a paper or grant is an important process. It also takes a lot of time, at least if done properly. Is it reasonable to expect already overworked individuals to carry out this demanding task out of the kindness of their hearts? The anonymity of refereeing means that even public recognition of their contribution is denied. So, in a spirit of the 'devil's advocate', why not, together with a more open system of reviewing, publish the names of the referees in the paper – say in the 'acknowledgements' section? And why not reward those hard-working referees for their efforts in some tangible way (for example, book/record tokens, travel vouchers, free electronic access to the journal etc.)? Academics are renowned for their cheap labour compared to, say, a solicitor who might expect to be paid £100-200 per hour for providing comparable skills, but some tangible token of their efforts could only be for the good.

In case anyone's listening, mine's a pint (real ale preferred). Or three.

Len Best

Ann Silver

As Chairman of the Executive Committee, and on behalf of The Society, I would like to thank Ann Silver for her enthusiastic chairmanship of the Benevolent Fund for the past 4 years. Ann has ensured that The Physiological Society has been able to support many individuals.

In a past issue of *Physiology News* (**56**, 40), Ann reviewed the mission of the Ben Fund, which was established in 1976 when the Council was asked if The Society could help the widow of a young Member whose son had special needs. Itself a charity, The Society may not give away its money but it can support the administration of the Ben Fund. This means that *all* donations to the Fund can be used to help what the Trust Deed calls those in 'necessitous circumstances' whose work, at any level, has contributed to the 'advancement of physiology'. I am certain Ann would appreciate Members making a donation using the forms available on The Society's web site or from the London Administration Office.

At our last meeting, David Brown, FRS, was appointed as the next Chairman of the Benevolent Fund.

Giovanni Mann

The Benevolent Fund

The raffle held at the Manchester Meeting in April raised £36 for the Benevolent Fund. The winner was Douglas Bovell (Glasgow Caledonian University).

At the Annual General Meeting of the Fund on 26 April David Brown was elected a Trustee; he had been serving as a co-opted member of the committee since the AGM in 2005. He was also elected Chairman in place of Ann Silver who had completed her 6 year term on the Committee of Trustees.

The Benevolent Fund will be holding a fund-raising raffle at the Main Meeting at UCL. The prize will be a choice between a Fortnum and Mason's food hamper or a case of Laithwaite's wines.

David Greenfield

1917–2005

David Greenfield, who died on 17 November 2005, had been the Foundation Dean of the Faculty of Medicine and Professor of Physiology at the University of Nottingham for 15 years from 1966-1981. He was Dean of the first new British medical school of the 20th century. Greenfield was also a distinguished physiologist. He had held the Dunville Chair of Physiology at Queen's University Belfast (1948-1964) and the Chair of Physiology at St Mary's Hospital Medical School. He is remembered for his gentle but firm determination, generous open-mindedness and rigorous attention to detail.

Born in Wallingford in 1917, David Greenfield was educated at Poo!e Grammar School and St Mary's Hospital Medical School. He is believed to be the first student at St Mary's to take an intercalated BSc Honours degree. He qualified in medicine in 1940. After resident appointments, including that of House Physician to Sir George Pickering, he joined the Department of Physiology at St Mary's as a junior lecturer. He told colleagues later that he was greatly influenced by A St G Huggett and G W Pickering. There he studied the circulation in human limbs, and collaborated in work on the haemodynamics of the foetal circulation. His research on the effects of acceleration and enhanced gravity on the circulation led to an association with the Institute of Aviation Medicine at Farnborough.

In 1948, at the age of 31, Greenfield was appointed to the Dunville Chair of Physiology at Queen's University of Belfast in succession to Henry Barcroft who had pioneered research into the human peripheral circulation. The Department attracted many brilliant young medical scientists. Greenfield was always able to get the best out of staff and to inspire great loyalty. Of those whose science he nurtured during the 16 years of his tenure of the Chair, eight subsequently occupied chairs and, of these, six became Deans of medical schools, and one was twice a Vice Chancellor. One became President of the American Heart Association. An intercalated honours degree in physiology was started, and the graduates have held important posts. Greenfield and his colleagues laid the foundations for our understanding of the neural control of the peripheral circulation. Modern treatments of vascular diseases are derived from this fundamental work. It is a measure of his own and his staff's enthusiasm that they were constantly presenting papers building and demolishing hypotheses at Society Meetings in London at a time when the journey from Belfast entailed a sea crossing and long train journey.

During 1963-64 he worked in Julius Comroe's department in the San Francisco Medical Centre, University of California. He invented and developed a technique for testing cardiovascular reflex function (lower body negative pressure) which became used extensively by NASA. This work was of great importance for our understanding of how the human circulation can withstand first the accleration and then the weightlessness of space travel. Greenfield has never received the credit for this that he deserved.

In 1964 Greenfield returned to St Mary's as professor, but plans were developing to start a new medical school in Nottingham. Sir George Pickering became the chairman of the University's Medical School Advisory Committee. In 1966 David was appointed to be Dean of the new school. It was a unique opportunity. It was the first new medical school of the 20th century in the UK. There were of course, problems. Nottingham had been chosen partly because it was in a seriously under-doctored part of the country and was in urgent need of a large new hospital, which would serve as the main teaching hospital for the school. Unfortunately, legal problems over site acquisition delayed the start of the building of the hospital until 1971, and integral with it the accommodation for the medical school. However, the school was committed to accept students in 1970, so temporary accommodation had to be used, and in the early years all clinical teaching was in existing hospitals with inadequate space and facilities. It needed enthusiasm, commitment, confidence and improvisation to start the school in such circumstances. Fortunately, these qualities were to be found among the doctors already in Nottingham and a team of young enthusiastic foundation professors who would develop a medical school with a different approach. The students, when they arrived in 1970, were exposed to patients from the first week of training and an intercalated degree was established for all. Greenfield was re-elected Dean for a succession of 3 year terms until he retired in 1981. The new school was by then firmly established with an annual entry of 130, and the University Hospital and Medical School buildings were complete, though not yet fully commissioned.

When Greenfield retired, the Medical School was firmly established in its permanent accommodation and the dream of 1966 had become the Queen's Medical Centre, which was opened by the Queen in 1977. This was his outstanding achievement: it proved to be a notable international success, both clinically and academicaly. To mark his involvement, the medical library was named The Greenfield Library. Three hundred and eighty five Nottingham doctors had qualified, the local clinical services had improved out of all recognition and a new medical curriculum copied by several other medical schools, established.

Greenfield was a member of the editorial boards of most of the

cardiovascular journals, a member of the MRC until 1977, then medical member of the University Grants Committee and Chairman of its Medical Subcommittee. He was also a member of the General Medical Council.

He travelled widely, even well into retirement, advising many universities planning new medical schools, most notably the Chinese University of Hong Kong, the University of Kuwait and the Sultan Qaboos University, Oman. He was a member of the Hong Kong University and Polytechnic Grants Committee.

He was made CBE in 1977, followed by the Order of St John in 1978 and the Order of Sultan Qaboos in 1986. He held the Honorary DSc from The Queen's University, Belfast and the Honorary LLD of the University of Nottingham. In 1987 he was elected an Honorary Member of The Physiological Society.

David Greenfield married Peggy Duane in 1943, when she was theatre sister to Mr Tom Holmes Sellors at Harefield Hospital, and she gave David unfailing support until her death in 1999. Their son, Peter, is a computer scientist, and their daughter, Catherine, a poet and author. There are two grandchildren.

Robert Graham
David Banks
Peter Fentem

Personal recollections of David Greenfield's years in Belfast

In 1948, when David Greenfield arrived in Belfast as a young man to succeed Henry Barcroft in the Chair of Physiology, I was a preclinical medical student. He so impressed me by his enthusiasm for his subject that, when the opportunity to take an intercalated BSc presented, physiology seemed the obvious choice. Thus began one of the most formative year in my life and I remain everlastingly grateful for the way it opened my mind.

The 16 years David spent at Queen's were vintage years, not just for him, the medical school and the University, but also for the interest in physiology and medical science it generated in the minds of young medical students and graduates. The upsurge of local interest in physiology led to a flowering of the Department. A flourishing BSc Honours School was established. Many medical graduates coming to the department for research experience were so attracted by its intellectual excitement and rigour that they changed plans and embarked on a career in academic physiology.

One of the main reasons for this was David's charisma. Though personally modest, unselfish and self-deprecating, he was intensely loyal and supportive to his juniors and was indefatigable in encouraging and helping them to reach their full potential. He built up their self-confidence, stimulated them to think independently, and delegated responsibility and credit to them whenever possible. He inculcated a family ethos in the department that bound its members together in common purpose, so carrying on a Barcroft tradition. His wife Peggy was particularly helpful in fostering this ethos through the motherly interest she took in all the members of staff and their families. She was a wonderful entertainer. The friendships and loyalties built up during those years lasted for life. It was an ideal environment for young academics to see what it takes to run happy and successful departments. Many of those trained there later reproduced a similar style in departments in other parts of the world.

With David's philosophy, anyone could do anything if they gave it sufficient thought and effort. No problem was insuperable. He will be remembered for his integrity, courtesy, enthusiasm, common sense and determination underpinned by an enormous capacity for hard work. He had excellent manual skills in the workshop and drawing office; the equipment he made was known for its ingenuity, simplicity and robustness and his diagrams were famous for their clarity.

Scientifically, the Greenfield years at Queen's were very productive. He continued Barcroft's interests in the human peripheral circulation and thereby maintained the department's international reputation. The standard test for assessing the circulatory reflexes of astronauts is based on Greenfield's work on the effects of lower body suction on man

David, and many of those influenced by him, were to have considerable influence on medical education and its management. David himself introduced many new ideas as Foundation Dean in the new medical school at Nottingham. He also played an important part in the foundation of the new medical schools at the Chinese University of Hong Kong, the Sultan Qaboos University in Oman and the University of Southern Rhodesia (now Zimbabwe) in Salisbury (now Harare). One of his lecturers, John Shepherd, who joined the staff of the Mayo Clinic, was selected as the Foundation Dean of the new undergraduate medical school that was set up there. He has had a profound effect on the academic development of the Clinic. Another of David's lecturers, Bob Whelan, was appointed to the Chair of Physiology in the University of Adelaide in Australia and subsequently was elected Dean of its Medical Faculty. Later he was appointed Vice-Chancellor at the universities of Western Australia at Perth and finally Liverpool in the UK. As with David, his experience and integrity made him a much sought-after member of local and national committees.

One of David's MRC Fellows, Bob Coles, was elected Clinical Dean at the University of Bristol. Another of his lecturers, Darty Glover, went to Australia to head Physiology at the University of New South Wales and was elected Dean of its Medical School in Sydney for several successive terms. In Belfast, Gary Love, Robin Shanks and I, all former BSc students and lecturers in the Department, were elected Dean of the Medical School at Queen's over a 15 year period. All of these would happily acknowledge how much David's influence had moulded their outlook and career...The collective contribution they made to medical education over the years was considerable.

David's modesty and habit of self-deprecation may have resulted in his true national and international contribution to medical education not receiving all the recognition it deserved. His style was to give credit for his achievements to others while down-playing his own role. Self-advertisement and self-promotion were completely foreign to him. Perhaps only those colleagues who knew him well recognized fully his truly remarkable qualities. Such qualities are in short supply today and will be sadly missed.

Ian C Roddie
Honorary Member, The Physiological Society

Autar Paintal

1925–2004

A personal memoir

Autar Paintal was one of the most distinguished physiologists to emerge from India, probably the most distinguished. The internet will give 236 references to him in <0.31 sec. There one may find detailed accounts of his work by a wide range of admirers.

Aside from his outstanding excellence and incisiveness as a physiologist, it was his grace and ever youthful sense of fun and mischief that endeared him to so many friends around the world. The well chosen photograph of him on the Vallabhbhai Patel Chest Institute web site where he worked from 1964 just about shows that twinkle in the eye, and his 'love of fun and mischief'. It is reproduced here. There is the man so many of us admired. He would have been delighted to find himself on the internet and especially to find that he was available on e-Bay in a list that includes 'new & used electronics, apparel, collectibles…autar paintal dsg accountants…holo holo…' and so on. Especially 'holo holo' would have appealed, an item closely listed near to him for sale. Similarly he is often to be found as an 'adobe acrobat' which would have provoked more glee.

With the award of a Rockefeller Fellowship, Autar Paintal arrived in Edinburgh in 1951 to work for a PhD under David Whitteridge. He spent several months first building an electrophysiological rig with ex-army electrical parts (with circuits from CJ Dickinson's book and guidance from 'Jock' Austin – both brought by DW to Edinburgh from Oxford).

His research uncovered many aspects of innervation through the vagus nerve of the structures within the body cavity, especially perhaps through his work on the heart and lung receptors. Some would say his discovery in 1955 of the J receptor in the lungs was his most important contribution.

I am not so sure for it is arguable that the most far reaching and most widely applied discovery he made was in Edinburgh (1951–1953) where he showed that one could record from nerve fibres, and dissect them under liquid paraffin. This technique, so simple in conception, has been taken up and used by neurophysiologists around the world. It immediately superseded frequent irrigation of the nerve with saline as in the early work of Adrian or the steam-box in which tissues were kept to prevent drying of the nerves. With that original apparatus, dissection was very difficult. Paintal's advance changed the way we all did experiments on nerve and made those experiments so very much easier. Furthermore, the method allowed much finer dissection than would otherwise be possible, for the nerve strands do not dry out. Thus smaller and smaller nerve fibres could be studied.

Another of Paintal's innovations was to short-circuit David Whitteridge's very elaborate indirect ways of localizing cardiac/pulmonary vagal afferent endings in the anaesthetised animal by fearlessly opening the chest and prodding about the heart and lungs with a glass rod. A fine example of direct observation and experiment.

With his PhD, he returned to India; but not, as expected, to Lucknow University – where he had obtained his MD (or MB). He would not go back to the Lucknow Medical College Physiology Department because he did not approve of their employment policies, but instead took a research position in Kanpur, at the Indian Army medical centre.

This failure to return to Lucknow got him into trouble with the Rockefeller Foundation: they had allowed him to take his electrophysiological equipment there but as a penalty for not returning to the parent institution, as required by the terms and conditions of his award, he was not allowed to take his rig to Kanpur. Some believe they were not going to be seen as supporting the Indian army. So he had to build everything again from scratch, in spite of the lack of parts and the absence of funds for importing anything from overseas: only someone with his fierce determination to get on with his research and sheer tenacity in overcoming endless bureaucratic hurdles throughout his career in India could have done it.

Maybe the association with a military institution had advantages for him, such was his skill, for he would have had access to military surplus apparatus. Think of those radar sets, amplifiers and power supplies, etc. In London at this time physiologists and other scientists scoured the army surplus and second hand stores in Lisle Street, Soho, in the same way.

I came to know Autar Paintal through The Physiological Society and we met often in the UK and from time to time in India. His distinction never obtruded in his interactions with colleagues old and new such was his openness.

He was politically incorrect as we would now term it, and in some ways politically incompetent, though he rose to the highest levels in Indian science, maybe because he was so straightforward. His sense of fun and his political incorrectness showed itself after a Physiological Society dinner in Magdalene College, Oxford where he gave the vote of thanks. He told how difficult it was to do science in India, and similar strictures apply throughout the world. Monday was the day after the weekend, Tuesday would be a religious celebration day, Wednesday one played games in the afternoon, Thursday was a Saint's day, and on Friday no self respecting Indian like himself could possibly do an experiment with the weekend imminent. Of course, it was not like that, and certainly not for him. He was devoted to science and pursued his subject with absolute integrity, he did

not countenance dissembling and was always straightforward. This quality no doubt occasionally led to trouble for him.

Many years later, as head of the Indian MRC, he made the headlines when, aiming to prevent the spread of AIDS to the subcontinent, he strongly urged Indian women to avoid making love to foreigners. This view was not widely applauded.

In his role as an organiser my experience of Paintal in operation was in India particularly at the time of the Physiological Congress in Delhi when he organised a meeting in Srinagar. He knew how to make administrative systems work. Many of us arrived at the airport in Delhi but some were delayed in Mumbai (Bombay as it then was). Paintal moved up and down the line quietly instructing us to make our check-in as slow as possible by misplacing our tickets, fumbling with our identifications, searching for our luggage. In short we were to behave like more than usually incompetent academics. This combined with the need to have every paper stamped and approved by various officials delayed our take off to such an extent that the Mumbai group arrived to travel with us.

He had developed to a fine degree the use of the technique of anger to make progress on a problem. It is always the case that to become angry is to lose control. However, to perform as if angry is sometimes useful in administrative life, but the technique should be used sparingly and always be under control. Paintal was a master at this. My wife and I were once in his office, even we feeling intimidated as he addressed some unfortunate down the telephone. So soon as he had his way, he switched in a flash to his normal charming self, unruffled by the previous maelstrom.

His widespread international recognition is typified by his appearance with rather a stern image in Россицкая Акademия Hayk as a Foreign Member.

Always he was, whatever the circumstances, an intensely serious scientist, interested in advancing knowledge, pursuing investigations with absolute integrity to the data, never fearing to criticise what he considered to be unworthy, and thus upholding the highest ethical standards.

Certainly he was widely admired and held in great affection by many physiologists and there are many who would have more stories to tell than me. Many knew him better, going back to the Edinburgh days, but perhaps no one enjoyed being with him more. We cannot imagine how much more than us his family must miss him.

I am grateful to Kres Krnjevic for his comments, especially on the Edinburgh days.

Tim Biscoe
Honorary Member

Deceased Members

The Society also reports, with regret, the deaths of **D L Ingram** and **J A Bateman**.

Doug Ingram was a Member from 1963–2001 and J A Bateman joined The Society in 1935, making him one of our longest serving Members.

We hope to carry obituaries in a future issue of *Physiology News*.

(Nicol et al. continued from p. 33)

representative of the systems studied. Equally important, cognitive brain research often requires highly trained animals. By maximising the data obtained from each animal, we reduce the number of animals needed – a duty of any bioscientist.

In summary, MEA techniques alone do not guarantee successfully understanding the brain, nor do they make other techniques obsolete. They are a promising supplement aiming to bridge the gap between imaging and single-cell studies. The brain has a century old track record of encrypting its functional principles. A combined strategy incorporating behavioural, imaging, single cell and MEA techniques will play the central part in deciphering the code. The rest is down to the ultimate tool – our brain. After all, it takes a thief to catch a thief!

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Hanno Fischer
Andrew J Tate
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Excitatory amino acid transmission in health and disease

By Robert Balázs, Richard J Bridges and Carl W Cotman. 2006 Oxford University Press. 368 pp, £49.00 (hardback). ISBN 0-19-515002-3

This is an up to date, very well researched and well written book on glutamate and the ways it contributes to signalling in the CNS through a diversity of receptors. The authors have succeeded in producing a lucid, well organised and fundamental account of a complex area, profusely illustrated by Cheryl A Cotman.

The opening chapter gives an overview and perspective and sets the scene for the remaining 11 chapters, five of which deal with ionotropic glutamate receptors and another with metabotropic glutamate receptors. Then follows a fascinating chapter on glutamate transporters through which glutamate is sequestered into cellular compartments and which regulate its intracellular concentration. Five distinct subtypes of excitatory amino acid transporters have now been identified and their disruption may lead to glutamate excitotoxicity perhaps associated with degenerative diseases such as amyotrophic lateral sclerosis and Alzheimer's disease. In addition, three vesicular glutamate transporters have now been identified which may regulate the vesicular content of glutamate at synapses and this leads into a chapter on the molecular organization of glutamate receptors in the postsynaptic density, which contains a 'supramolecular complex of interacting anchoring proteins, glutamate receptors, signaling molecules, and cytoskleletal proteins'. This complex serves a wide variety of purposes allowing synaptic modulation and plasticity, which are considered in detail in the penultimate chapter of the book. The final chapter deals with the roles of glutamate and glutamate receptors in neurological diseases.

The book is readable, well-produced and should appeal to everyone, from advanced undergraduates upwards, who has an interest in this area.

Bill Winlow

The Wellcome Trust launch party to celebrate the publication of *The Journal of Physiology* archive

Under the *Medical Journals Backfiles Digitisation Project* the archives of 17 British journals connected with medicine, physiology and biochemistry are being put online at PubMed Central. *The Journal of Physiology* is part of this project. Representatives of the various journals gathered at the Wellcome Trust's headquarters in London for a launch party on 11 May. The project is a joint venture of the Wellcome Trust, the Joint Information Systems Committee and the National Library of Medicine (NLM) in Bethesda, Maryland, whose National Center for Biotechnology Information (NCBI) runs PubMed Central.

The photos show: Top (left): William Large (centre, Editor-in-Chief of *The Journal of Physiology*) with Carol Huxley (Managing Editor) and Jonathan Goodchild (Senior Production Editor); Top (right): Mark Walport (Director of the Wellcome Trust); Centre (left): Robert Kiley (Wellcome Library); Centre (right): Prem Kumar (Deputy Editor-in-Chief of *The Journal of Physiology*) with Giovanni Mann (Chairman of The Society's Executive Committee); Above (left): Carol Myers (NCBI), Martha Fishel (NLM); Above (right): Tilli Tansey (Wellcome Institute for the History of Medicine).

See also *A century (and more) of physiology now online* (p. 40).

SOCIETY MEETINGS

For more information visit The Society's web site at http://www.physoc.org

2006

University College London, UK
5–7 July
Physiological Society Main Meeting, Annual General Meeting and Young Physiologists' Symposium *From molecules to behaviour*.

Ribeirao Preto, Brazil
27–30 August
Joint International Meeting with the Brazilian Physiological Society and Young Physiologists' Symposium.

Heidelberg, Germany
13 September
Focused Meeting *Control and modification of excitation-contraction coupling in healthy and diseased muscle.*

Charles University, Prague
21–23 September 2006
International Workshop *Lung function in health and disease*.

Bristol, UK
4–5 December
Focused Meeting *New developments in stress physiology.*

2007

Glasgow, Scotland
8–12 July
Joint Meeting of The Physiological Society, Biochemical Society and British Pharmacological Society.

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

FEDERATION OF EUROPEAN NEUROSCIENCE SOCIETIES

Vienna, Austria
8–12 July 2006
http://www.fens.org

8th INTERNATIONAL SYMPOSIUM ON NEUROBIOLOGY AND NEUROENDOCRINOLOGY OF AGING

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

BRITISH ASSOCIATION FOR PSYCHOPHARMACOLOGY

10–16 September
Nottingham
Experimental Psychopharmacology Summer School
http://www.bap.org.uk

EUROPEAN COUNCIL FOR CARDIOVASCULAR RESEARCH (ECCR)

29 September – 1 October
La Colle sur Loup, Nice, France
http://www.eccr.org

IUPS

Kyoto, Japan
27 July – 1 August 2009

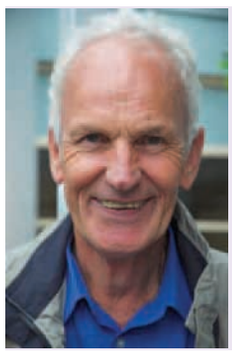
UK
July 2013
http://www.iups.org

The Xth Oxford Conference

Modeling and control of breathing – integration in respiratory control: from genes to systems

Lake Louise, Alberta, Canada
19-24 September

Further information is available at
http://www.ucalgary.ca/~oxford06
or email
oxford06@ucalgary.ca



Uwe Proske, a member of the Editorial Board of *The Journal of Physiology*, pictured earlier this year at a symposium to mark his retirement from the Department of Physiology at Monash University, Australia.

MOLECULAR TECHNIQUES FOR LIFE SCIENCES WORKSHOPS

Manipulating Nucleic Acids

28 August - 1 September
A five day practical workshop to introduce participants to techniques used in molecular biology investigations and to facilitate development of core molecular biology skills. Cost: £870 (Standard), £740 (CPD Accredited).

PCR Theory and Practice

4-8 September 2006
22-26 January 2007
A five day course to introduce participants to this core technique covering the basics to quantitative Real-time PCR. Cost: £870 (Standard), £740 (CPD Accredited).

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Fax: +44 (0)141 331 3208
Email: mtls@gcal.ac.uk

UK SPIKE TRAIN ANALYSIS WORKSHOP

28 August - 8 September
University of Newcastle, UK
A major international workshop to bring together individuals from neuroscience, mathematics, computing and statistics to work on developing novel analytic tools.
http://www.ncl.ac.uk/ion/spiketrain

Notices for the autumn 2006 issue of *Physiology News* should reach the Publications Office by 30 June. Please send contributions to lrimmer@physoc.org