PN
Physiology News

Issue 88 / Autumn 2012

Reports from Physiology 2012

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Putting the brain into brainstem

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Putting the debate in context

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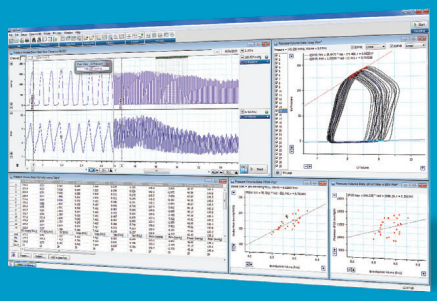

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Contents

Welcome to the Autumn edition of *Physiology News*.

Physiology News

We welcome feedback on our membership magazine, or letters and suggestions for articles for publication from Physiological Society Members. Please email **magazine@physoc.org**

Physiology News is one of the benefits of membership of The Physiological Society, along with reduced registration rates for our high-profile events, free online access to The Physiological Society's leading journals, *The Journal of Physiology* and *Experimental Physiology*, and travel grants to attend scientific meetings. Membership of The Physiological Society offers you access to the largest network of physiologists in Europe.

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Editorial

The original Society was primarily a male, medical (albeit liberal) grouping – we have come a very long way towards the inclusive participation of everyone who calls themselves a physiologist.

Picture Credit: Kate Faxen

Jonathan Ashmore

On 26 May 1876, the opening declaration of a newly formed society stated, confidently, as its Clause 1: *'This Society is called "The Physiological Society"'*. It is still there in the constitution. It is a testament to the strength of our organisation that we are still discussing the excitement and the desires of the science that created The Society. There have been changes in how we are organised. There have been, not surprisingly, momentous changes in the scope and volume of the science. There have been equally profound changes in membership and participation. The original Society was primarily a male, medical (albeit liberal) grouping – we have come a very long way towards the inclusive participation of everyone who calls themself a physiologist. Physiology has spun off disciplines which have sometimes grown even larger than their parent. But above all we are held together by a common passion to understand, at every level, the mechanisms and principles that constitute the startling functioning complexity of living entities.

So what are the priorities of The Society? To be blunt, the profile of physiology as a discipline has receded a little even during my career in science: physiology departments in the UK have been merged and lost individual identities; '-omics' sciences have grown, often without the breadth of a 'big picture' of animal and human function, but always underpinned by physiology. We need to address that, particularly when the need for understanding how the many startling recent developments in biomedical science can be integrated for the good of all. In terms of a membership, The Society has remained relatively static, at least in the UK. We need to address that as well. There is huge potential for making collaborations in many spheres that underpin translational medicine, nationally and internationally, simply because The Society has held a strategic place in international science for well over a century; doors are opened by our position and we can and should use that.

The three current areas of The Society's activities deserve special mention: our new premises, our new publication and our plans for IUPS 2013. Thanks to a group chaired for the past 18 months by Mike Spyer, we shall soon move into new permanent space in Farringdon, London EC1. It is the first time, I believe, that we have been in the position of not just leasing, but owning our accommodation. It will be a major asset, not just financial, but to bring the activities of The Society all under one roof. It will provide valuable lecture and meeting room space to develop what we offer.

Secondly, in collaboration with the American Physiological Society, we are just about to launch our new open-access journal, *Physiological Reports*. It is scheduled to launch at the beginning of 2013. The publication will have the muscle of Wiley-Blackwell, our publishers for *The Journal of Physiology* and *Experimental Physiology*, and it will have a major impact on the field.

Thirdly, after the extremely successful Physiology 2012 – the Edinburgh meeting which attracted over 1000 attendees – we are aiming high for IUPS 2013. The meeting will take place in Birmingham's International Convention Centre and we are expecting an attendance of over 3500 people. IUPS 2103 is already shaping up to be really stimulating and nobody reading this can afford to miss it.

As incoming President I know that I stand on the shoulders of others. Mike Spyer has for the past two years been an outstandingly successful Society President, initiating many new projects. I have mentioned only a few here. As Deputy President, I saw how he managed a large number of difficult assignments with a steady hand. Above all, he has steered The Society into a position where, despite all the uncertainties that surround learned societies today, we are able to make the best use of our resources to the benefit of our membership in the UK and internationally. Richard Vaughan-Jones, stepping in as the new Deputy President, The Society's team in the new 'Hodgkin-Huxley House', and everyone on the Executive Committee and Council will be making sure that the next period will be as exciting and as stimulating as it can possibly be.

Finally, I extend a warm welcome to the new members of Council. The Society elected six places on Council at the Annual General Meeting in Edinburgh. The Council is now 22 strong and we look forward to discussing – sometimes heatedly – the many topics that come up in the course of the year. The members of Council and I are there to respond to your concerns and to generate an exciting programme of meetings and activities which should touch everyone. This, after all, is **your** Society.

See p.44 for Jonathan's Top Ten Papers.

Annual General Meeting

The 2012 Annual General Meeting (AGM) was held at the Edinburgh International Conference Centre on Thursday 5 July 2012. The meeting was chaired by Richard Ribchester, Professor of Cellular Neuroscience at The University of Edinburgh.

The meeting saw Jonathan Ashmore, Bernard Katz Professor of Biophysics at University College London (UCL), succeed Mike Spyer as Society President.

Mike, Emeritus Sophia-Jex Blake Professor of Physiology at UCL, said: "I'm very pleased to be able to hand over to Jonathan. As well as being a close colleague of mine, he is a man of immense standing in the field and has the vision to take The Society on to great things. I enjoyed my time as President immensely and am glad to leave The Society growing in strength. I'll continue to be an active Member because of the very real value of the organisation to physiology and to working physiologists."

Other new appointments are:

- Deputy President: Richard Vaughan-Jones
- Chair, Education & Outreach Committee: Blair Grubb
- Chair, Policy Committee: Mary Morrell

Members at the meeting heard reports from the Editors-in-Chief of *The Journal of Physiology* and *Experimental Physiology*. Members were updated on the purchase of premises for The Society and were told of the intention to rename the new building 'Hodgkin-Huxley House', and permission for this has now been granted by the local planning authority.

Membership fees for 2013 were announced – see p.4.

Full minutes of the meeting are available online at www.physoc.org/annual-general-meeting-2012-minutes.

Incoming and outgoing Council members

The six Members elected to Council are:

- Blair Grubb
- Ken O'Halloran
- David Thwaites
- Richard Vaughan-Jones
- Judy Harris
- Lucia Sivilotti

The Society offers thanks to the outgoing Council members:

- Mike Spyer
- Jeremy Ward
- Patricia de Winter
- Louise Robson
- Susan Jones
- Ian McGrath

Honorary Members

Six individuals were awarded honorary membership of The Society. The new Honorary Members are:

- Richard Axel and Linda Buck, elected because of their discovery of the genes that encode olfactory receptors
- David Colquhoun, elected because of his contribution to our understanding of the synaptic mechanisms of single ion channel function
- John Nicholls, elected because of his work in laboratory teaching courses for young scientists through the International Brain Research Organization, his acclaimed book *From Neuron to Brain*, as well as his comprehensive studies of the leech nervous system and research on neural regeneration and respiratory rhythm
- Venki Ramakrishnan, elected because of his work on the structure and role of the ribosome
- Semir Zeki, elected because of his multi-disciplinary work exploring the neural basis of aesthetic appreciation and artistic creativity.

History and Archives stand celebrates Edinburgh physiologists

A portrait medallion of Carl Ludwig, the famous German physiologist and inventor of the kymograph, William Rutherford's own 'Ludwig' kymograph, and a Lewis–Mackenzie polygraph (the precursor of the 'lie detector') comprised the star attractions on the History and Archives Committee stand at this year's Main Meeting, Physiology 2012. These pieces were generously loaned by the University of Edinburgh's Centre for Integrative Physiology.

Other items on display included a large annotated photograph showing all the attendees of the 1923 *International Congress of Physiological Sciences* held in Edinburgh, with an accompanying letter from the Edinburgh Police chief describing the arrangements for checking passports of the attending 'aliens'. Our thanks goes out to Jane Haley, Neuroscience Scientific Manager at the University of Edinburgh, who put in much of her own time to clean and prepare all these items for display.

In addition to Edinburgh's historical memorabilia, there was a rolling slideshow of photos of noted physiologists. These pictures were the legacy of Martin Rosenberg – a long-standing member of the History and Archives Committee who died last October – and a testament to the immense contribution he made to recording the history of physiology.

The stand also celebrated the lives of two successive Edinburgh professors of physiology: William Rutherford and Sir Edward Sharpey-Schafer. Along with Rutherford's kymograph, we exhibited the first volume of the journal Sharpey-Schafer founded: the *Quarterly Journal of Experimental Physiology* (today's *Experimental Physiology*).

Dafydd Walters talks to Bob Banks at the History and Archives Stand, at Physiology 2012, in Edinburgh

One thousand delegates at Physiology 2012

Left to right: David Paterson, Jere Mitchell, Peter Ratcliffe and Bengt Saltin at Our Dynamic Earth

Mike Spyer, as Society President, presents Peter Ratcliffe with the Annual Review Prize

Around 1000 delegates attended The Society's annual Main Meeting in Edinburgh, 2–5 July. As well as 21 symposia, 109 oral communications and 365 posters, exploring many compelling areas of physiological research, delegates were also treated to plenary lectures from some of the most notable figures in the field.

The Public Lecture was delivered this year by Gareth Leng, Professor of *Experimental Physiology* at the University of Edinburgh. For the first time, we broadcast our annual public lecture to an online audience of over 700.

Peter Ratcliffe, who delivered the Annual Review Prize Lecture, said: "I had a great time in Edinburgh and was impressed with the science presented there, in particular a range of new approaches combining molecular and integrative physiology. I really enjoyed delivering the Annual Review Prize Lecture."

GSK Prize Lecturer, Holly Shiels, said: "The whole meeting was a great experience and Edinburgh was lovely. I particularly enjoyed meeting colleagues in the crossed theme symposium on alternative animal models and catching up with old friends at the conference dinner. I'll definitely be attending IUPS next year in Birmingham!"

For a full report on the conference, see p.14.

Diane Lipscombe delivers the Joan Mott Prize Lecture

The Society announces the winners of the 2012 Rob Clarke Awards

The Society is pleased to announce the winners of the first Rob Clarke Awards, which were introduced this year to recognise excellence in physiology research at undergraduate level. Eighteen finalists were selected for a Rob Clarke Abstract Award and invited to present their abstract as a poster to a team of judges at Physiology 2012 on 4 July 2012. Each finalist also received £200 to support their attendance at the meeting and one year's free membership of The Society.

Six finalists were each awarded a Rob Clarke Presentation Award.

The winners were:

- Lucy Gentles (University of Liverpool)
- Adam Keen (University of Manchester)
- Hannah McKay (University of Oxford)
- Sejal Modasia (King's College London)
- Jonathan Prager (University of Bristol)
- Mina Skelly (University of Bristol)

Award winner, Adam Keen, said: "It was a great opportunity to speak to people, many of whom gave interesting ideas about further studies for me to do relating to this work."

See p.12 for a report from prize winner, Mina Skelly.

Rob Clarke Prize judge, Louise Robson, announces the winners

Policy Corner

Welcome to 'Policy Corner', a new regular feature designed to update our Members on the policy work being carried out by The Physiological Society.

'Policy' sounds rather dull, but is vitally important for individual academics, departments and institutions, as well as for the health of physiology as a discipline. Our job is to influence decision-making individuals and bodies, ensuring the voice of physiology is heard. We do this through meetings with government departments and Members of Parliament, submissions to inquiries held by parliamentary select committees, and engagement with other learned societies and professional bodies.

Our work over the last year includes responses to consultations (including a HEFCE consultation about the Research Excellence Framework, and one about commercialization and translation of research), organising an event about new legislation for the use of animals in research, and attending meetings at both the UK and European parliaments.

We want to inform you about developments which will impact on your work, and we're also hoping that it will place you in a position to become more involved. We want to ensure our policy work represents the interests of our Members, and to utilise the expertise contained within our Membership to inform consultation and inquiry responses,.

A lot of policy work, by necessity, is carried out in short timeframes; consultations and inquiries are often launched unexpectedly, with submission deadlines only weeks away. It won't always be possible to ask for input into these through 'Policy Corner', and in this case we will do so through our email newsletter.

Additionally, we are continually gathering names to add to our membership expertise database, allowing us to contact interested Members directly if an issue arises.

If you have any questions about the work we carry out, any of the updates on this page, or to add your details to our database, please don't hesitate to contact our Policy Manager on policy@physoc.org

Accreditation of bioscience degrees

The structure of the Society of Biology (SB) accreditation programme has been finalised, with the creation of three broad streams; Molecular Aspects of Bioscience, Ecological and Environmental Sciences, and Whole Organism Biology. A separate accreditation stream will remain for degrees containing a significant *in vivo* component.

Whilst The Physiological Society is adopting a cautious approach towards accreditation of all bioscience degrees, we have been engaging with SB, helping to develop the criteria.

Sport and Exercise Science and Medicine

In May, the House of Lords Science and Technology Committee launched a short inquiry on sport and exercise science and medicine, aiming to better understand if and how public health can be improved as part of the Olympic legacy.

Committee clerks contacted The Society, asking us to recommend academics to participate in a seminar and inviting us to submit a response to the inquiry.

The report produced by the Committee extensively referenced our response, including concerns about there being no obvious lead research council for exercise physiology and sports science.

More information, including The Physiological Society response and Committee Report, can be found on our website, www.physoc.org/our-impact

House of Lords HE in STEM consultation

This July, the House of Lords Science and Technology Committee published their report, *Higher Education in Science, Technology, Engineering and Mathematics Subjects*; the result of an inquiry last year .

The recommendations made by this report are not limited to the widely reported obligatory post-16 maths education, but also include a call for better data collection on the supply and demand of science, technology and mathematics (STEM) graduates, and a proposal to set up an expert group to look at STEM postgraduate provision.

The report also highlighted our concerns about the possible compound effect of various policy reforms on the provision of stand-alone masters degrees.

Our response to the inquiry can be found on www.physoc.org/our-impact

Legislation on the use of animals in research

At the time of writing, the Home Office hasn't yet released the bill containing the new legislation required to update or replace the Animals (Scientific Procedures) Act 1986.

Watch our website for updates.

Can you help us?

The Physiological Society are trying to engage with as many MPs as possible about the use of animals in research, hoping to dispel myths of covering cats with lipstick. We'd like Members who use animals in research to contact their MP and discuss the nature and the benefits of their work, including how it furthers our understanding of how disease mechanisms and biological systems operate, and the development of potential treatments and medicines for both animals and humans.

Twenty-five years of the Children's Health and Exercise Research Centre

Craig Williams
Director of CHERC

The Children's Health and Exercise Research Centre (CHERC) at the University of Exeter is celebrating its 25th anniversary as a centre devoted to the study of the exercising child and adolescent and the promotion of young people's health and well-being. It is recognised as one of the world's leading centres for paediatric exercise physiology. Research produced by CHERC has had a national and international impact on raising public awareness of child health issues and has shaped policy development. The centre played host to the international bi-annual Pediatric Work Physiology conference in 2011, having previously hosted it in 1997 – the only research centre to have this honour twice.

Founded on a desire to acquire child-specific data, Neil Armstrong identified for the first time the prevalence of coronary risk factors in British children and examined them in relation to cardiovascular fitness and habitual physical activity. The physical activity data demonstrated that many children had adopted sedentary lifestyles. Physical activity patterns and cardiovascular fitness were subsequently investigated in relation to diet, body fat, obesity, visceral fat, diabetes and hypertension.

Findings widely disseminated through the national/international popular press and academic journals and conferences have significantly influenced policy, on issues related to children's health and well-being, and were recognised by the award of the Queen's Anniversary Prize for Higher Education. The Anniversary Prize was the first to be awarded in the exercise and sport sciences.

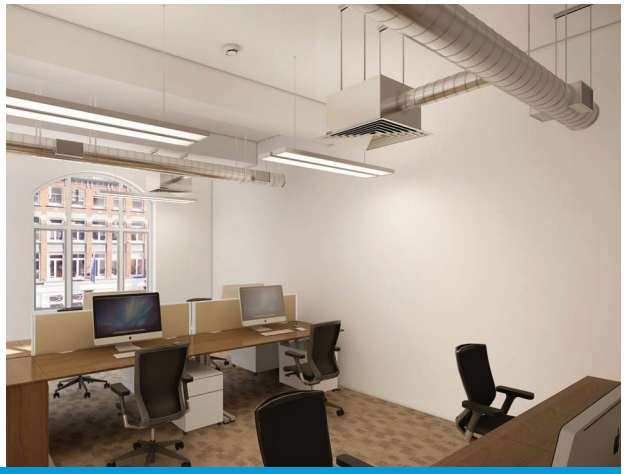
Over the years, CHERC studies have raised numerous methodological problems regarding the measurement and interpretation of physiological variables during growth and maturation and the examination of these issues has been a major focus. For example, we challenged the conventional interpretation of aerobic fitness during growth and maturation in a series of studies that found that, when body mass was appropriately controlled, boys' peak oxygen uptake progressively increases with age and girls' values increase into the teen years with no evident decline into young adulthood. Using multi-level modelling to analyse longitudinal data, on 12–17 year olds, we demonstrated that both chronological age and stage of maturation were explanatory variables of peak oxygen uptake independent of body size and composition and that conventional analyses had obscured the independent relationship between aerobic fitness and maturation. Other research into training, over-training (Richard Winsley) and sport-specific laboratory and field-based research has informed and underpinned consultancy work with numerous national sport governing bodies, the International Olympic Committee, and Premier League Football and Rugby Academies.

Currently, basic research has initiated the use of breath-by-breath respiratory gas analysis and magnetic resonance spectroscopy to study the oxygen uptake ($\dot{V}O_2$) and phosphocreatine (PCr) kinetics of children during the rapid changes of exercise intensity which characterise most sporting activities. Alan Barker's work on the measurement and interpretation of $\dot{V}O_2$ and PCr kinetics data has used these advanced experimental techniques to provide new insights into the physiology of exercise during growth and maturation. To date, our findings have shown that the transitions from rest to both moderate and heavy intensity exercise and of incremental exercise to exhaustion suggest that there is an age- and maturation-dependent change in muscles' potential for oxygen utilisation, with children having a greater mitochondrial capacity for oxidation than adults.

An important aim of CHERC is to raise the profile of children's health and well-being regionally, nationally and internationally. To date, the team has been invited to present its research to conferences in 42 countries and has presented over 100 workshops to teachers, students and academics in Europe, Asia and the Americas. The Centre through providing the first PhD training in the UK in paediatric exercise science has produced a new generation of researchers and educators. Thirty seven graduates of the CHERC are currently teaching, researching and promoting the subject around the world. Internationally, former members of the Centre are in academic posts in France, Portugal, Canada, USA, Mexico, Hong Kong, Singapore, and Malaysia. The first taught MSc programme in paediatric exercise physiology was developed in the Centre and it is proving very attractive to UK, EU and international students.

Finally, the importance of acquiring child-related data is as important today as it was 25 years ago. There is still much to be done and we look forward to the challenge of the next 25 years with youthful enthusiasm!

A home for physiology



Proposed designs for Hodgkin–Huxley House

With ownership of 30 Farringdon Lane now secured, The Society has engaged the services of office design specialist Peldon Rose to oversee the fit out.

The Society is a small, but diverse organisation, and the demands on the new premises reflect this. Staff must be housed in a way that optimises working processes and takes into account the needs of individuals.

But, of course, we expect much more than this from the future 'Hodgkin–Huxley House': as well as being an exemplary working environment, the new premises will aspire to be a home for physiology. Provision for focused scientific meetings and public engagement events will be integral to the building, making best use of the space for events that can be formal or casual, big or small; from staff and committee meetings, to lectures and even receptions. The interior design is expected to do no less than reflect the energy and vigour of The Society, from its founding to the present day, and we are looking at how we best reflect our history in the new environment. We shall have full copies of our journals on display (but protected) and we are exploring the possibility of a display of old physiological equipment.

The Farringdon Offices will also, in part, be an investment in what is an up-coming area of London with Farringdon CrossRail arriving in 2018. In addition there are opportunities to generate revenue, as we will let two floors and allow hire of the on-site meeting rooms and auditorium.

Dawn McAdam, Project Designer at Peldon Rose, said: "The relocation project for The Physiological Society is interesting in that it is a mixed-use environment, which not only has to house their various departments in a pleasant working environment, but also be a public space in which to engage the membership as well as members of the public with a high level of adaptability.

"We love the challenge that this type of project brings and finding the best design solutions to solve them.

"At Peldon Rose we take the time to understand our client's individual requirements. We are working with The Society to realise aspirations, bringing in experts from our team to assist in each choice, to provide an inspirational yet functional space that motivates, inspires and ultimately improves their business."

YPS2012: Integrative Physiology

Andrew Morton
University of Edinburgh

On 2 July 2012, the Centre for Integrative Physiology at the University of Edinburgh hosted the Young Physiologists' Symposium as a satellite event to Physiology 2012. Fittingly for the venue, and in an effort to include a diverse audience of young physiologists from across the spectrum of topics covered by The Physiological Society, we made integrative physiology our theme. In three sessions, our programme progressed through multiple levels of investigation of physiological systems, from cellular physiology, to physiology in tissues, networks and circuits, concluding with *in vivo* and systems physiology.

More than 120 delegates squeezed into Hugh Robson Building to participate in the packed schedule of talks and poster presentations. The standard of presenting and audience engagement was fantastic throughout. This made our lives easier as session chairs, but very difficult as judges of the competitions for best talk and poster.

At our drinks reception, in accordance with long-standing Physiological Society tradition, the women cleaned up: Louise Hickey, The University of Bristol, won our image competition with her beautiful image 'The great wave of neurones'; the prize for best poster went to Melina Figueiredo, also of The University of Bristol; the award for the best talk went to Julia Schiemann of the University of Edinburgh.

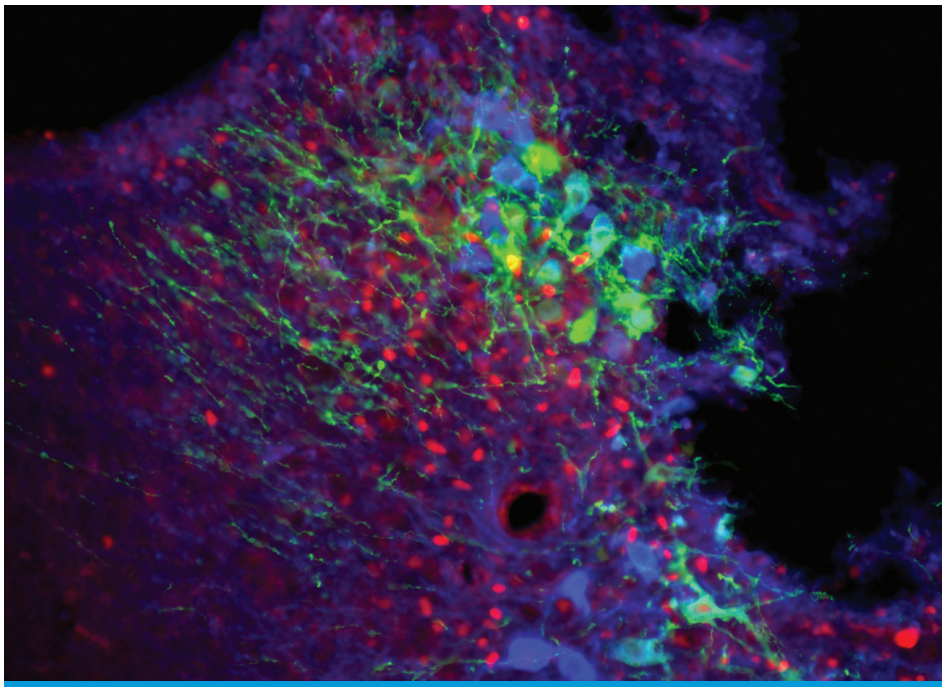
In her fantastic talk, 'An exciting *in vivo* function of K-ATP channels in dopamine midbrain neurons is potentiated in Parkinson Disease', Julia did an incredible job of presenting more than six years' worth of elegant experiments from her time at Goethe-University Frankfurt, Germany, in just 10 minutes.

Melina's poster, 'Novel optogenetic tools for control of astrocytic $[Ca]_i$' described neat methods for targeting a calcium translocating channel rhodopsin to the endoplasmic reticulum, allowing optical control of calcium release from internal stores in astrocytes.

And so it was that a great wave of young physiologists emerged from the Young Physiologists' Symposium to join the body of the kirk at Physiology 2012.

YPS2012: Integrative Physiology was organised by myself, Peter Duncan, Amira Mahmoud and Steph Barnes, all PhD students at Centre for Integrative Physiology, The University of Edinburgh.

In addition to the support of The Physiological Society, we would like to thank the following external sponsors: Wellcome Images, Vector Laboratories, Axiope, Digitimer, World Precision Instruments, Dunn Labortechnik, Quadratech and New England Biolabs.



Prize-winning image, 'The great wave of neurones', Louise Hickey

Physiology 2012: The undergraduate experience

Mina Skelly
University of Bristol

Mina Skelly presenting her poster at Physiology 2012

Physiology 2012 was a wonderful experience. The meeting was a fantastic opportunity to engage with a range of people and discover the amazing research currently being undertaken throughout the country. With such a diverse range of subject areas, one minute I found myself attending a communication on olfaction and fear, and the next a presentation on obesity. Each presentation provided me with easy access to cutting-edge findings that I would otherwise have been unlikely to come across. Being part of an audience with active research scientists and academics, my colleagues and I were able to sit and appreciate the way in which challenging and innovative questions could help to direct research, giving us an insight into the value of these sorts of meetings. It truly made us realise how much further we have to go in our level of thinking – giving us something to aspire to!

The main purpose of our attending Physiology 2012 was to present posters based on the research we had carried out at our respective institutions. There were 15 undergraduates present, from universities across the country. Whilst presenting, we were approached by teams of judges to whom we explained our research. The questions asked by the judges were, at first, simple, but then became rapidly more challenging and really pushed us to think. The wide variety of specialisations and backgrounds of the judges meant the questions arose from many angles. Although nerve-racking, it was valuable to be presented with thought-provoking questions, which made us look at our own research in a new light. It was great for gathering ideas as to what may have affected our findings and ways in which we could improve our experiments, both in terms of design and additional evidence we might need.

Finally, after the presentations, the winners of the poster prizes were announced, and I was thrilled to be amongst them!

In addition to the Main Meeting, there was an entire day dedicated to young physiologists, where many PhD students presented their research in the form of poster presentations and oral communications. These were accessible to us as guest undergraduates, which made it an encouraging day. It also gave us the opportunity to interact with physiologists somewhat closer to our level than many of the speakers and delegates at the Main Meeting. With posters, prizes, nibbles and drinks, this day was a fantastic ice-breaker.

As part of the Rob Clarke Award for undergraduates, we were able to attend the Society Dinner. With wonderful food and wine, it was a special occasion where we could interact on a more personal level, with physiologists from around the world. All were very approachable and it was an excellent chance to make friends and network.

Although Physiology 2012 was not intended perhaps for undergraduates, we certainly got a great deal out of being given this chance to come. Great thanks to the late Rob Clarke, and to those who made it possible for us to attend Physiology 2012.

The Society will host the Rob Clarke Awards again in 2013, with final judging taking place at the IUPS congress in Birmingham.

2012
Forthcoming events

11 Oct

Models of experimental pain: opportunities and challenges. Central London. www.nc3rs.org.uk/event

17 Oct

Career Crossroads to Career Activist. Angel Gate, London. www.bps.ac.uk/meetings/137a2b6df1f#GeneralInformationand Registration

11–13 Dec

Metabolism & Endocrinology Themed Meeting Royal Society, London, UK www.physoc.org/me2012/

Supporting China in 2012.

1 – 4 November 2012, Suzhou, China

Following the success of the 2008 meeting in Beijing, The Society is supporting the Chinese Association of Physiological Sciences (CAPS) meeting at the Suzhou International Expo Center. Famed as the 'Venice of the Orient', Suzhou is renowned for its beautiful stone bridges, pagodas and classical gardens. The Society has sponsored two symposia:

Identifying physiological and pathophysiological roles for ionotropic glutamate receptor subtypes

Friday 2 November 2012
Chairs: Ying-Shing Chan (Hong Kong, China) and David Wyllie (Edinburgh, UK)

Speakers:

- Ying-Shing Chan (Hong Kong, China) Developmental plasticity: The engagement of glutamate receptors in mediating spatial coding
- Ian Forsythe (Leicester, UK) Glutamate receptor function in auditory nuclei
- Susan Jones (Cambridge, UK) NMDA glutamate receptors in midbrain dopaminergic neurones
- Jianhong Luo (Hangzhou, China) Adaptor protein APPL1 couples synaptic NMDA receptor with neuronal pro-survival phosphatidylinositol 3-kinase/Akt pathway
- David Wyllie (Edinburgh, UK) NMDA receptors: new insights from studies of chimeric receptors

Cardiovascular regulation in health and disease

Saturday 3 November 2012
Chairs: David Paterson (Oxford, UK) and Xiaorong Zeng (Luzhou, China)

Speakers:

- Ming Lei (Manchester, UK) Role of Pak1 signalling in cardiac regulation and its therapeutic potential in heart disease
- David Paterson (Oxford, UK) Targeting Cyclic Nucleotides to Rescue Cardiac Sympatho Vagal Phenotypes in Cardiovascular Disease
- Julian Paton (Bristol, UK) The Blood Brain Barrier and Control of Arterial Pressure
- Ruiping Xiao (Beijing, China) The roles of beta2 adrenaline receptor signaling pathway in the heart
- Zhuan Zhou (Beijing, China) Electrochemical recording of evoked norepinephine release from sympathetic nerves in rodent cardiac slices

Raising our profile at Neuroscience 2012

12 October – Journal of Physiology symposium

14–17 October – Exhibition at Earnest N Morial Convention Center

New Orleans will be the setting for an awe-inspiring 30,000 + participants who regularly attend this annual neuroscience jamboree. *The Journal of Physiology* is sponsoring a satellite symposium entitled Size matters: formation and function of GIANT synapses, being held in the Neuroscience Center of Excellence, 8th Floor Conference Room, 2020 Gravier Street from 8.15 am on Friday 12 October 2012.

Registration is free and seating is limited, so those interested are asked to contact Chunlai Wu to register: cwu@lsuhsc.edu.

We will also be formally promoting *The Journal of Physiology* (and JP Neuroscience) at Booth 242 during the main conference. If you are attending we would like to know and would really love to see you during the meeting itself. Indeed, if you would like to act as a *Journal* and Society ambassador at the stand, please email our Events Director, Nick Boross-Toby, at nboross-toby@physoc.org prior

Meeting Notes

Physiology 2012

2–5 July 2012, Edinburgh, UK

David Wyllie

Meetings Secretary, The Physiological Society

The Society's Main Meeting returned to Edinburgh this year, for the first time since 1996, attracting 1000 physiologists from all over the world.

Planning for this year's meeting began over two years ago when the Meetings Committee took the decision to break with the traditional university venue, opting instead to hold the meeting in the excellent facilities of the Edinburgh International Conference Centre – indeed more that 90% of those responding to our post-meeting survey agreed with this description. We experienced what some might call 'typically Scottish weather' throughout the week, and having the event all under one roof avoided rain-soaked dashes between lecture theatres.

A Young Physiologists' Symposium was held the day before the start of the main programme (see p.11 for a full report). The GSK Prize Lecture by Holly Shiels later that evening showed that research isn't always restricted to four walls in a university, but can offer travel to exotic locations to seek out species that are models for physiological research.

All the plenary lectures are now available to view on The Society's website. The lectures by Cori Bargmann, Diane Lipscombe and Peter Ratcliffe demonstrated how the elegant use of optogenetics in *C. elegans*, structure-function studies of voltage-gated calcium channels and the elucidation of biochemical pathways used to sense oxygen provide us with detailed understanding of systems, cellular and molecular physiology, with each lecture highlighting their exquisite control mechanisms. Jere Mitchell's Paton Prize Lecture was a wonderful lesson in how we should always be aware of the work of those who precede us – the pioneering work of early physiologists shows us that measurements made many decades ago laid the foundations for current research. We all have a responsibility to disseminate our research to wider audiences and Gareth Leng's Public Lecture 'The Loving Brain: monogamy to maternity' was a superb example of how this should be done. His outstanding presentation described his research with wit and humour and conveyed his research in a manner that held the attention of all.

Approximately 400 oral/poster communications ensured that there was plenty on show for everyone and much was made of the opportunities for discussion and feedback during these sessions. Oral and poster presentation prize winners are listed on The Society's website. New for this year was a dedicated session for undergraduate students to present research from dissertation studies – I congratulate all who were selected to present their work and hope that this sparks their interest in a career in research (see p.12).

This year's meeting included 21 symposia, the largest number so far, with research themes having at least one dedicated symposium each

day. Though themed, it was hoped that many symposia would attract wider audiences to allow interaction across disciplines. One colleague commented: "One of the pleasures of the main Physoc meeting is learning things about related fields. Since obesity is closely linked with obstructive sleep apnoea, I try to keep up to date, and the Edinburgh meeting was a perfect opportunity. Kevin Murphy gave an excellent talk on obesity and the latest on appetite regulation – I will never again look at a pizza in the same way!" To reflect The Society's commitment to teaching and education we included a symposium on this theme within the main programme. Following on from this symposium, Eugene Lloyd of the University of Bristol delivered the Otto Hutter Teaching Prize Lecture 'Dangerous assumptions and misconceptions: Can physiology teaching help to improve patient safety?' Eugene emphasised the importance of basic physiology in clinical teaching. As both a lecturer and clinician Eugene was able to give an insight into what happens when medical students and junior doctors don't understand basic physiology, and also some more uplifting accounts of when they do.

Again, from the feedback survey, the symposia we programmed appear to have been well received. Nevertheless, we are open to suggestions and one which was raised with me on several occasions was to include shorter presentations within symposia, as we do in our Themed Meetings, to allow early-career physiologists to share the stage with more senior colleagues. This will be done at IUPS 2013 but I welcome comments as to whether we should adopt such a format at the Main Meeting.

Delegates were entertained at the Welcome Reception in The Hub's magnificent Main Hall by George Heriot's School Pipe Band, while the Society Dinner was held at Our Dynamic Earth. Unfortunately the spectacular setting of our dinner venue could not be fully appreciated as the infamous east coast 'haar' shrouded us from the sights of Holyrood Palace, the Scottish Parliament buildings, Salisbury Crags and Arthur's Seat.

Next year The Society hosts IUPS 2013 which will serve as our Main Meeting, but the call for symposia proposals for Physiology 2014 will open later this year. If you have not attended the Main Meeting for several years, I urge you to re-acquaint yourself with our flagship event and see what excellent value it is for everyone, no matter their career stage. A typical comment I received from many attendees at Physiology 2012 was how much they appreciated attending a meeting of a size that means that everyone is treated as an individual, but which gives attendees a terrific opportunity not only to hear about the latest world-class physiological research, but provides a first-class forum for networking and discussion.

I end by acknowledging the participation, work and efforts of all – this made Physiology 2012 a tremendous experience. Thank you.

Meeting Notes

Physiology@Newcastle

8 March 2012, Newcastle, UK

Megan Webster, Nichola Conlon and Git Chung

Newcastle University

Like most universities, Newcastle University has gone through several rounds of restructuring over recent years. Old departmental structures have disappeared and, with them, so has the Department of Physiological Sciences. There are many benefits to the new structure, but it does make it a little more difficult to talk 'physiology'. With this in mind, David Thwaites organised an afternoon of oral presentations to bring together individuals from across the faculty to present their most recent findings. The afternoon was funded by a generous award from The Physiological Society, with additional funding from the School of Biomedical Sciences.

Around 130 physiologists gathered in the University Research 'Beehive', including undergraduates, postgraduates, postdocs and academics (and even a Dean). The first session kicked off with a series of talks by Newcastle graduates on their varied careers following graduation.

The next session highlighted the quality and diversity of physiological research at Newcastle University, with nine short presentations by current PhD students and postdocs. Research interests ranged from recurrent urinary tract infections in females (Marcelo Lanz) to the production of an *in vitro* model to study brain network oscillations in health and disease (Claire Gillougley). Cyril Elefteriou provided an interesting insight into biotechnology with a talk about his quest to find a suitable nanomaterial for epi-retinal implants that will hopefully allow for the correction of retinal degeneration diseases in the future. Other presentations described work from the whole animal (Karen Fisher, Neuroscience; Anne-Marie Hynes, Genetic Medicine) to the molecular (Aiqing Chen, Cellular Medicine; Noel Edwards, Cell & Molecular Biosciences) on topics from brainstem function, to vascular smooth muscle and renal disease. There were two prizes for the most popular presentations, won by Mark Turner for his lucid summary of his work on the effects of hypercapnia on CFTR-dependent HCO_3^- secretion in human airway epithelial cells, and Natalie Bell for her compelling insights into possible therapies for neuroblastoma by targeting of calcium signalling pathways.

The day was finished off by a presentation by Paul Sharp, a Newcastle physiology graduate now at King's College London. The theme of his talk was the regulation of dietary iron absorption, which touched on the governing processes behind the intestinal absorption of iron, its regulation in the body, and the crucial role iron plays in a number of physiological functions.

The main objectives of Physiology@Newcastle were to provide an opportunity for physiologists of all ages to meet and chat about their work, to give young physiologists the chance to showcase their research findings, and to encourage and inspire would-be scientists into the discipline. It seemed to be a success on all counts. Nineteen undergraduates signed up as Members of The Society after the event.

Left to right: Natalie Bell, Mark Turner, Nichola Conlon, Git Chung and Megan Webster

Meeting Notes

60 Years of Hodgkin and Huxley

12–13 July 2012, Cambridge, UK

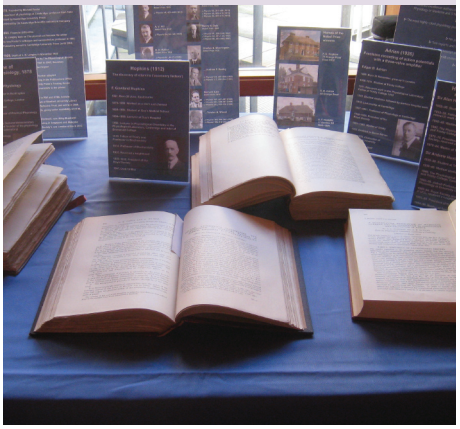
Jonathan Goodchild

Senior Production Editor,
The Journal of Physiology

It is 60 years since Alan Hodgkin and Andrew Huxley published in *The Journal of Physiology* their classic papers giving the mechanism of the nerve impulse. To celebrate and review progress in the field, a two-day symposium was held on 12–13 July at Trinity College, Cambridge (where they were students, fellows and, successively, the Master), organized by Simon O'Connor along with James Bower (University of Texas Health Science Center, San Antonio), Michael Häusser (University College London) and Idan Segev (Hebrew University, Jerusalem).

The Physiological Society and *The Journal of Physiology*, among others, provided sponsorship, and *The Journal* put on a display featuring the first volume of 1878 along with volumes open at the papers of the Cambridge Nobel Prize winners, Hopkins (1912), Adrian (1926) and of course Hodgkin & Huxley (1952), accompanied by photographs of their homes and timelines of their lives.

On the first day, the symposium delegates joined family members for the unveiling of a plaque to Adrian, Hodgkin and Huxley on the wall of the physiology building where they worked, followed by a historical lecture by Bertil Hille (University of Washington at Seattle). In the evening, the symposium dinner was held at Trinity College, with an after-dinner speech by Ian Glynn, Emeritus Professor of Physiology and Fellow of the college.



Casey van Breemen and prize winners

Meeting Notes

Vascular & Smooth Muscle Physiology Themed Meeting

6–8 December 2011, Edinburgh, UK

Mark Evans

Centre for Integrative Physiology, The University of Edinburgh

When the call for a Vascular and Smooth Muscle Themed Meeting was circulated to members of The Society, it seemed like a great opportunity to highlight an area that I consider to be of major importance to the field, and one which has received far too little attention over the last 30 years, since the first insight was provided by Casey van Breemen. I refer, of course, to the proposal that membrane-membrane junctions less than 100 nm across may provide nanodomains for regulated calcium signalling in smooth muscle. I called Graeme Nixon at the University of Aberdeen and the idea took shape – we would try to develop, through a symposium, the idea that a cell could not regulate processes as diverse as contraction, migration and gene expression without them. We submitted our proposal and, to our surprise at the time, it was accepted. But would the invited speakers be willing to travel to Scotland in December?

Either the 'inclement' Scottish weather of December 2010 had been forgotten, or there was some enthusiasm for the possibility of spending Christmas at a good hotel in Edinburgh, because all invitations were accepted with enthusiasm. Thankfully there was little snow, although a fairly significant arctic wind (hurricane, to be christened 'Baw Bag') did disrupt travel on the final day.

The Physiological Society's Events Team seamlessly engaged with our symposium sketch and delivered what proved to be a very successful programme of events that centred on the historic Surgeon's Hall. Daniel Defoe was an early visitor to the associated museums in 1726, and wrote in his *Tour thro' the whole Island of Great Britain* that the 'chamber of rarities' contained many curious things too numerous for him to describe. I guess he may have said the same had he attended our symposium.

The symposium commenced on Tuesday 6 December, when Casey van Breemen introduced the concept of cellular nanospaces. The programme then developed more smoothly than we had anticipated, with all speakers falling into line as if through prior discussion. I introduced the evidence we had provided in support of Casey's original proposal that nanojunctions may exist between the plasma membrane and the sarcoplasmic reticulum, that this was separated from a cytoplasmic space in which calcium promoted smooth-muscle contraction, and threw in a handful of lysosome-sarcoplasmic reticulum junctions for good measure. For their part, Mike Zhu provided the two pore segment channels, David Beech the TRP channels and Ian Parker the IP_3 receptors. The stage was then set for Nicola Fameli to blind everybody with the maths that 'proved' that only nanospaces, and not microdomains, had the capacity to support regulated and compartmentalised calcium signalling.

On day two, John McCarron and Graeme Nixon escorted those gathered towards an appreciation of the plasticity of smooth muscle cells as they switch to a proliferative phenotype, ably assisted by Maria Gomez and Teresa Perez-Garcia. Casey van Breemen then rounded off the day by integrating the identified nanojunctions in a model that was generally accepted by most, if not all those present – as indicated by an important and final comment from Martin Bootman: "Smooth muscle is more complicated than cardiac muscle." The chair surprisingly agreed, and we moved on to enjoy some fine dining in the Victorian splendour of the Playfair Hall.

The selected oral and poster presentations were of the highest standard and added to what was a vibrant meeting. The prize winners were as follows:

- Oral Communication Competition Winner: Junxi Wu, University of Strathclyde
- Runner up: Thomas Jepps, St George's, University of London
- Poster Competition Winner: Lynn McKeown, University of Leeds
- Runner up: Oluseye Ogunbayo, University of Edinburgh

This symposium proved to be a great success with all those who attended and stimulated much discussion. I was therefore pleased to be informed that this topic was selected as a symposium for IUPS 2013, in Birmingham. We hope to see you there.

Current ethical issues in animal research

The use of animals in research is a matter of substantial public interest and can generate impassioned debate which includes the ethics of using animals for experimentation. Dominic Wells reviews specific ethical issues in the scientific use of animals and puts the debate into context.

Dominic Wells
Royal Veterinary College, UK

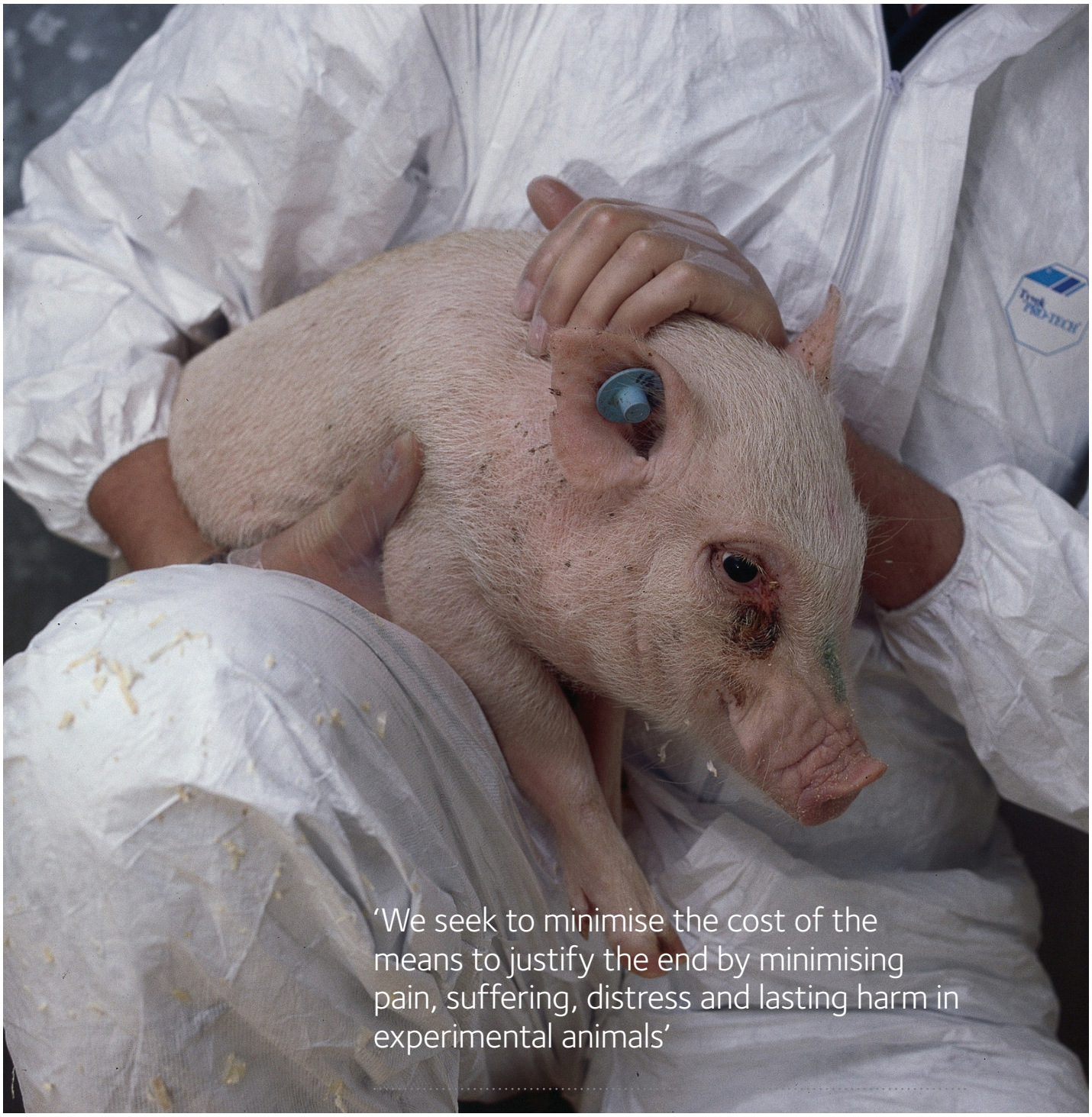
Ethics can be defined as a framework in which moral decisions (what is right or wrong) can be made. There are two main schools of thought: Consequential (utilitarian) or Deontological (intrinsic).

Within the animal rights movement two of the best-known philosophers are examples of these different schools of thought. Peter Singer is a utilitarian ethicist who argues that there is no valid reason for separating man from all the other animals, which he calls a speciesist view with close similarities to racism and sexism. Consequently animals have rights in a similar way to man. His seminal book, *Animal Liberation*, was published in 1975 (1) and he is regarded by many as the founding father of the animal rights movement. However, while animals have similar rights to man, the rights of the individual can in some cases be subsumed for the greater good, although this requires a very clear cost–benefit analysis. In contrast, Tom Reagan is a deontological ethicist who argues animals have intrinsic worth and rejects the concept that the ends can justify the means. Consequently animals have intrinsic value as do humans: for example, this argument is presented in (2). Thus, in this school of thought, the use of animals in research can never be justified.

Interestingly, the earliest clear statement on the ethics of animal experimentation occurred at the time of the debate about the rights of man. In his 1789 *Introduction to the Principles of Morals and Legislation* (3), the utilitarian philosopher Jeremy Bentham queried the use and abuse of animals. He wrote: "The question is not, Can they reason? nor, Can they talk? but, Can they suffer?". It should be noted that Bentham had no fundamental objection to animal experiments provided that the goal was of benefit to humanity and that there was a reasonable prospect of achieving that goal.

In *Animal Liberation* (1), Singer codified the concept of animal rights in the context of human rights as: "Animal rights means that animals deserve certain kinds of consideration – consideration of what is in their own best interests regardless of whether they are cute, useful to humans, or an endangered species and regardless of whether any human cares about them at all (just as a mentally-challenged human has rights even if he or she is not cute or useful or even if everyone dislikes him or her). It means recognizing that animals are not ours to use – for food, clothing, entertainment, or experimentation".

How do we relate these ethical views to the use of animals in research? Our attitude to



ethical questions in animal research stems from the relationship of human society with all animals. Animals are used for food, transport and entertainment as well as research. In many societies ill-treatment of animals is not accepted, although this is by no means universal. Thus, in general we take a modified utilitarian attitude – ‘the end can justify the means’ or ‘the greatest good of the greatest number’, but crucially with humans given a greater worth than any other species – the speciesist view disparaged by Singer.

We seek to minimise the cost of the means to justify the end by minimising pain, suffering, distress and lasting harm in experimental animals. Thus, we aim to reduce the number of animals used in experiments to a minimum. We strive to refine the way experiments are carried out, to make sure animals suffer as little as possible. And we replace animal experiments with non-animal techniques wherever possible. These key tenets of humane experimental use of animals, often referred to as the 3Rs, were developed by Russell and Burch in their highly influential 1959 publication *The Principles of Humane Experimental Technique*.

The current Animals (Scientific Procedures) Act 1986 (4) relies on this modified utilitarian ethical judgement. The revised version that will come into force in January 2013, which incorporates changes associated with Directive 2010/63/EU, will continue the same approach. Each project must be assessed on a cost–benefit basis, by asking the question of whether the ends justify the

‘A strong case needs to be made that the studies are necessary and that the experimental aims are well defined and are likely to yield clear answers’

means. Experimental design should aim to reduce the costs (by application of the 3Rs) and critically evaluate the likely benefits. A strong case needs to be made that the studies are necessary and that the experimental aims are well defined and are likely to yield clear answers. The benefits may be for humans and/or other animals but there is a clear hierarchy, with no protection for invertebrate animals other than octopus and with cats, dogs, horses and primates being given special status of greater protection compared with other non-human mammals.

Genetically modified (GM) mice raise additional ethical questions. GM animals are the most rapidly growing element of animal use with more than 1.6 million GM animals and harmful mutants bred in the UK without other manipulations in 2011 (5) and this trend appears likely to continue to increase. It has been argued that GM violates the integrity of the organism’s genome. This is of course unacceptable in the deontological and questionable from the strict utilitarian view. However, the modified utilitarian view would argue that, in the absence of a harmful phenotype, there is no difference from wild-type in terms of the welfare of the animals, i.e. the animal is unaware that its genome has been modified.

Other human uses of animal

It is reasonable to ask why there is so much focus on animal experiments. Much of this may be due to the lack of public understanding of other uses of animals. The use of shock tactics of antivivisectionists and the ‘Yuk factor’ of some of the images used are partly responsible for the exaggerated emphasis on animal experimentation. There are many non-experimental uses of animals, for example, as food, clothing, transport, pets, sport and exhibition. The numbers used in non-experimental activities are huge. The UK uses 3.6 million animals in research annually (78% rodents, 15% fish) but UK meat and fish eaters consume 2.5 billion animals every year (6). This is nearly 700 times the numbers used in research yet it could be argued that consumption of fish and meat is not essential for human wellbeing, whereas at least some of the animal research is essential. Both utilitarian and intrinsic ethical arguments would suggest this use of animals for meat is the more important problem that should be tackled ahead of the use of animals in research. This disparity between animals used for food and research is even greater when considered on a world-wide basis. It has been estimated that 140 billion animals are killed for food every year (3000 times the number estimated for use in research worldwide). While the slaughter of domestic mammals and birds

‘It has been estimated that 140 billion animals are killed for food every year (3000 times the number estimated for use in research worldwide)’

may in many cases be reasonably humane, that cannot be said of most of the 90 billion fish killed worldwide each year, where suffocation is the most common cause of death.

Recreational uses of animals should also be considered in comparison with the use of animals in research. Fishing for game or coarse fish is a very popular pastime in the UK but, although it gives pleasure to many, it does not have major consequences in terms of human health. There is little doubt that fish feel pain and respond to it and so recreational fishing is less ethically justified than the use of fish in research. Sport involving animals often has a high attrition rate. As mentioned previously, horses receive special protection under ASPA legislation yet almost 50% of thoroughbred foals do not reach flat race training in the UK (7), as many suffer tendon injuries and fractures that impair their ability to perform. Again, the utilitarian argument would suggest that horse racing was ethically less acceptable than the use of horses in experimental research.

Very large numbers of animals are kept as pets and this is not without ethical consequences. For example, based on a survey of over 600 cat owners (7) it can be estimated that cats kill over 220 million vertebrate wild animals per year in the UK, the majority of them being small mammals. This is 60 times the number used in research. So decreasing the cat population, or keeping them indoors on a permanent basis, would have a greater impact on the loss of life than reducing the numbers of animals used in research, but is keeping a cat indoors for life infringing its rights?

What is the ethical way forward? Both Singer and Regan argue that we should not eat meat or fish or use animals in any way that cause them harm. So we should all be vegetarian and limit our harmful interactions with animals. That is philosophically an entirely reasonable approach. However, given our current modified utilitarian (speciesist) use of animals in non-research areas, much of the ethical debate about the use of animals in research is redundant.

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What price research?

We all know the need for refinement, reduction and replacement (the 3Rs) in animal experimentation, but it is little appreciated how the present over-strict bureaucratic regulation of biomedical research involving experiments on animals not only slows progress, but also blights careers.

John Coote and Olga Hudlicka

University of Birmingham, UK

In view of the Government announcement that it is updating UK law regulating research using animals to bring the UK in line with the recent EU directive (2010/63/EU), this is a good time to consider how bureaucracy can influence and affect science and scientists. To understand these issues it is important to rehearse the history of the topic.

An important feature of a civilized society is that it pursues the highest standard of care for the health of its human and animal population. Understanding the structure and working of living organisms has been pivotal to achieving this. Physiological knowledge and best practice of medicine and proper care of the ill are tightly linked. There have been many obstacles to achieving the present-day high standards of treatment, not the least by groups opposed to vivisection and by unsympathetic bureaucracy of governments and research institutions including universities. Other areas of science and scholarship have been less affected by such obstacles.

Biological research is essential for understanding the action of cells, organs and systems of the body. It is a demanding activity requiring great skill, dedication and a total commitment of time and effort. The advances are also dependent on non-medical sciences like chemistry, physics and engineering; for instance, chemists characterised and eventually synthesised nature's compounds such as digitalis, atropine, ephedrine or anaesthetics, which first were observed in the curing action of plants. More recently, high-power imaging devices, such as positron emission tomography and magnetic resonance imaging developed by engineers and physicists, have been part of the arsenal available for fundamental research and treatment of disease.

It is also worth remembering that the rapid advances of knowledge seen in the last century have depended on the landmark discoveries over the previous 200 years. During the 18th century the biologist or medical practitioner could look for practically no help from the natural sciences. For example, John Hunter (1728–1793), one of the most celebrated of all surgeons and a pioneer of scientific method during the 18th century, realized that he really needed to know the physiology to ensure the best outcome of his surgical intervention. He therefore carried out experiments on living animals and this had to be done without anaesthesia because the actions of ether or chloroform were not discovered for another 50 years (1846). These studies, techniques that seem very crude and cruel to us today, such as cutting nerves, tying off blood vessels or removing organs and observing what happens, were very important in providing knowledge that was very valuable to a surgeon, who daily was doing similar things on human patients (also without anaesthesia).

The 19th century witnessed an explosion of biological knowledge about the working of the animal body that was dependent on experiments on living animals. This was largely driven by the desire to know how things worked. The spin-off was that this led to major advances in health and management of disease. However, biomedical scientists and the public became rightly concerned about the pain and suffering inflicted on animals in unregulated experiments. In 1876 Parliament passed an act to regulate experiments likely to cause pain by introducing a Licence which also stipulated they could only be conducted under anaesthesia and with a view to increasing

‘It is little realized that the requirement for precise definitions and a clear purpose of the procedures to be used in a research protocol are so strictly regulated it can impede curiosity driven research’

'An important feature of a civilized society is that it pursues the highest standard of care for the health of its human and animal population'

physiological knowledge, or saving or prolonging life and alleviating suffering. The prime purpose of the act was to prevent animals suffering. Throughout the 20th century experiments on animals increased and there were many outstanding discoveries such as receptors controlling blood pressure and respiration, hormones, mechanisms of nerve conduction and transmission, cell membrane receptors and their pharmacology etc., providing huge medical benefits. However, the voice of moral philosophers, animal welfare and antivivisectionist groups became more strident because they considered the scope of the 1876 Act was not sufficiently well specified, leaving some important procedures open to interpretation. Too many animals were used, alternatives were not being seriously considered and reasons for experiments were not sufficiently well defined. On the other side, under the 1876 Act, researchers felt insufficiently protected from accusation of causing suffering or harm to animals. Those involved with biomedical research also strongly felt that the 1876 Act was insufficient to regulate animal welfare in light of new developments and discoveries in genetic and molecular biology that did not necessarily involve vivisection. For example, animals could be bred with genetic defects that altered organ function that had marked effects on their physiology. In 1986 Parliament approved 'The Animals (Scientific Procedures) Act (ASPA)' and this essentially governs experiments on living animals at present. Again the prime purpose of the act was/is animal welfare. The Act provides authority for specific work, rather than simply a list of what may be done irrespective of why and in what context. The enforcement of the Act meant that biomedical researchers in the UK were tightly regulated and the Act became a model for regulating all work in many other countries. Recently the European Parliament has adopted this strict approach and issued a directive on the ethical and legal requirements concerning the use of animals in scientific research in Europe that have now been transposed into UK legislation.

The regulation can be burdensome. Under the 1986 UK Act (ASPA), to carry out research involving animals, the researcher with relevant qualifications has to undergo training and to pass an examination before being granted a personal licence allowing them to carry out clearly specified, regulated procedures. Secondly, they can only work under a research project that requires a Project Licence approved by the Home Office. The Project Licence is a detailed description of the work they are intending, why it is needed, its purpose and the methodology. Here there has to be a serious consideration of the best methods which are embraced by the term *refinement* and the fewest number of animals needed, embraced by *reduction*. They must also consider carefully the need to use a protected animal or whether an alternative method could be used to achieve the aim, a principle embraced by *replacement*. Thirdly, the regulated procedures can only be carried out in a licensed, certificated designated place. The procedures are also classified according to severity in terms of pain, suffering, distress and lasting harm. Applications are subject to local ethical committee approval before consideration by the Inspectorate and final approval by the Secretary of State. Overall the process from start to finish can take a year

‘The truth is that many great discoveries have not been mission oriented, but have come about by curiosity to understand the physiology’

or more. The Project Licence has a limited life span of 5 years.

It is little realized that the requirement for precise definitions and a clear purpose of the procedures to be used in a research protocol are so strictly regulated it can impede curiosity driven research. Of course, it is necessary to have a clear plan of research, but this should have some built-in flexibility and should not always be directly linked to human or animal disease. The truth is that many great discoveries have not been mission oriented but have come about by curiosity to understand the physiology. A recent example is the major breakthrough in the treatment of drug-resistant hypertension (Dibona & Esler, 2010). A simple operation that destroys the nerves in the wall of renal blood vessels via a radio frequency transmitting current from a catheter inserted into a renal artery was shown to bring about a clinically significant reduction in hypertension. This procedure would not have been done but for a discovery in animal experiments fifty years ago. Then researchers were just beginning to wonder what the many nerves supplying each kidney did to its function (Astrom & Crafoord 1968). There was no intended purpose to determine if they could be contributing to a sustained morbid increase in blood pressure.

The new legislation does not allow procedures to be worded with sufficient freedom to accommodate minor variations. Changes may need further approval by local ethics committee and then by Home Office. It is well accepted that any project has to have given consideration to alternatives (replacement), numbers (reduction) and refinement. A problem is the rigidity of interpretation by Home Office Inspectors that can vary from one to another. It is an offence if the terms of the Licence (Personal or Project) are not followed exactly even if no harm has come to animals. Infringement of one or more conditions of the Licence can lead to prosecution (imprisonment of up to 2 years on conviction), or the Licence may be revoked (so terminating the studies) or a period of retraining may be required. The extent of the bureaucracy means that every researcher has to be alert to the danger of carrying out even quite minor changes in a procedure. This can happen to someone who has undergone a prolonged period of training in medicine, in dentistry, in science or even in veterinary surgery. Transgressions can result in severe disruption or complete loss of career. In fact, it is much less restrictive to do experiments on humans.

With the burden of the legislated restrictions and paper work and the constant threat of

animal rights campaigners, it is surprising that the desire to conduct experiments on living animals to advance biomedical knowledge has not been totally extinguished. It is, though, essential that such work continues because modern developments in cell and gene technology have not and probably will not lead to animal experimentation being superceded. For example, the new science of optogenetics enables genetically labelled cells to be selectively targeted by directed laser beams of light. This technique, shown to work so informatively on flies and simple animals, has considerable potential to manipulate cells in brain and heart or other organs in mammals, providing opportunities to explore the physiology as well as mechanism of disease. Thus, a genetic manipulation has not removed the need for studies on whole animals.

The law is there to prevent unnecessary harm to animals. Therefore, minor transgressions that do not affect animal welfare should be judged more sympathetically. In this context, it is worth considering a few cases in animal research that illustrate the often trivial nature of offences that attract the severest of penalties. These are hypothetical examples based on real cases. Say that a procedure stated, 'In an anaesthetized animal the stellate ganglion (which supplies nerves to the heart) will be exposed retropleurally via the space between heads of ribs 1 and 2 and injected with a toxin'. If, for control purposes, the toxin injection is omitted then an infringement is committed even though there is less damage to the health of the animal and, in the end, fewer animals are used. Of course, this should have been included in the procedure but the need may only have come to light during the study. Another example is vaginal smearing, an unlicensed procedure practised on a daily basis in high street pet shops or breeding establishments, has to have a Licence if it is part of a research project. So far so good, but if the procedure in the project does not state that it will be done on more than one occasion and the researcher does this more than once, assuming it is *de facto* or *causa sine qua non*, then this is considered an infringement.

We all understand the need for some restrictions. Apart from the three categories of licence the purpose of ASPA is to ensure animal welfare by stringently applying the three principles – replacement, reduction and refinement. Yet when considering compliance and infringement, many of the cases brought have not transgressed any of these nor have they meant that experimental animals have been mistreated.

What is perhaps not appreciated is that employers also impose a code of practice intended

‘With the burden of the legislated restrictions and paper work and the constant threat of animal rights campaigners, it is surprising that the desire to conduct experiments on living animals to advance biomedical knowledge has not been totally extinguished’

to comply with its legal obligations but also to protect itself from accusations of being soft on possible offenders. In practise, the staff are rarely supported by their employer and they are often more severely disciplined (dismissed or removed from certain duties). This occurs even when the infringement comes into a minor category. Thus, employers appear to ignore the main purpose of ASPA and the legal regulations. Recent exposure of poor nursing care and diagnostic mistakes in the medical profession in hospitals that have gone relatively unpunished serve to highlight the imbalance of justice and how human society loves its animals more that itself.

Subjection to the interpretation and impositions of law makers and employers is but one high price we pay for research. A further concern is an increasing demand for biomedical scientists to demonstrate how their studies help in understanding and treating disease. Researchers submitting projects for funding or papers for publication are under greater pressure than ever to come up with some exciting medical benefit of the work. However, the prime purpose of much research that may result in major clinical benefits has rarely been to cure a disease. We have already given the example of studies on the function of renal nerves. A more recent example of this is the work of Frances Ashcroft, the winner of the L’Oréal-UNESCO award 2012 for women in science. She explains that it was the urge to discover how the closure of a channel in a cell membrane resulted in secretion of a hormone that underpins her research. Her excitement at the result was because she had observed one of nature’s exquisite mechanisms. Subsequently the thrill of unravelling the DNA sequence that codes for the channel protein was the ultimate reward. This, of course, was made even better when later, in collaboration with Andrew Hattersley, it was shown how a mutation in a gene normally coding for the protein led to a rare form of neonatal diabetes. This then resulted in the discovery that sulphonylurea drugs were able to aid glucose in closing the ion channel and provide good clinical control of this early type of diabetes in children.

If you have read this far you may be wondering why it is that we have raised this topic in *Physiology News*. Are we just stirring the embers of an old debate? A reason is that many like us (until recently) will be poorly informed about the effects of legislation and the action of authoritarian institutions on the careers of individual researchers. Our concern is that the obstacles we have outlined will deter young scientists from whole animal research, and there will be a loss of skills. By the time the discoveries in molecular biology need to be verified in living bodies there will be no one left who would know how to do it.

In conclusion, the administration of the law should be simplified and based on the original principles, the advance of knowledge and welfare of animals.

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Putting the brain into brainstem

What goes on in the brainstem and why should processes normally associated with higher parts of the brain be found much lower?

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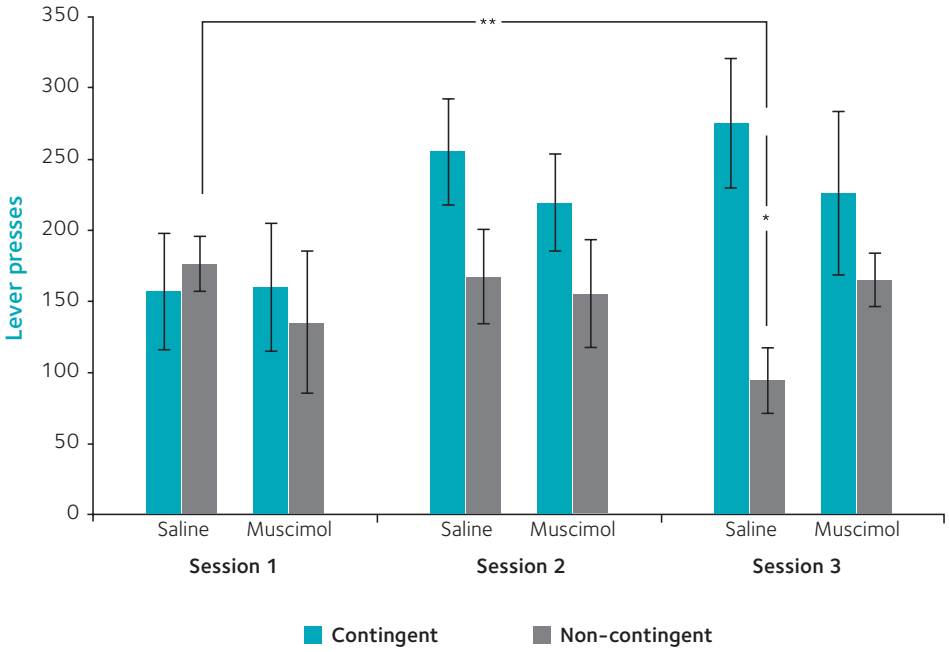
On the basis of experiments conducted in my lab we have concluded that brainstem functions are more sophisticated than previously thought, including critical processes of behavioural control. We argue that complex processes of learning and decision making are imperative for animals to thrive, and as such must be present in the oldest parts of brain – and we predict that when such processes go wrong, the results are catastrophic.

Visceral processes, respiration, arousal; semiautomatic skeletal functions, balance – familiar terms describing brainstem operations. In studying the pedunculopontine tegmental nucleus (PPTg), a small part of the mesopontine tegmentum, we have come to question whether these sorts of functions are enough to describe brainstem. The conventional view of PPTg is that it regulates locomotion and sleep, being described as part of the mesencephalic locomotor region and the ascending reticular activating system (Winn, 2008). However, in a series of experiments we have shown that rats bearing bilateral excitotoxic lesions of PPTg have deficits other than these. After recovery from surgery, lesioned rats have no impairment in locomotion, feeding, drinking, body weight maintenance or grooming. There is no dysfunction in normal sleep – REM or slow wave (Winn, 2008) – or in 'emotional' behaviour (Walker & Winn, 2007). But while lesioned rats seem normal, they actually have profound learning deficits.

The eight-arm radial maze (8ARM) tests spatial learning. For a random foraging task, rats were placed into the maze, with all eight arms open but only four baited with food – these four changed randomly trial by trial. Rats needed to find food without entering the same arm twice; the criterion for success was three consecutive days of testing with less than one error by the whole group. At the point when sham-operated rats achieved this, lesioned rats were at chance level, failing regardless of whether or not they were task-trained before surgery. However, lesioned rats' latency for first arm entry, and their speed from arm to arm, was not different to controls: their failure to perform properly was explicitly not the product of motor deficit (Keating & Winn, 2002). In other experiments we examined intravenous self-administration (IVSA) of drugs. Rats were equipped with intra-jugular catheters connected to a syringe pump, operated by the rat pressing a lever. Two levers were available, but only one delivered amphetamine – pressing the other achieved nothing. Control rats steadily increased pressing on the reinforced lever over sessions: they like amphetamine. Lesioned rats did not learn and were no better on the last session than on the first. Two further experiments added to this: first, if rats were pre-trained to lever press for food (that is, they made a lever pressing–reward association before being lesioned) then pressing for amphetamine was exactly like that of controls. Despite the lesion, they pressed correctly and recognized the rewarding value of amphetamine. Second, regardless of prior training, lesioned rats did not perform well on a progressive ratio schedule of reinforcement where the number of lever presses per reward increased throughout the test (Alderson *et al.* 2004).

Figure 1. Contingency degradation: rats were trained on a RR20 schedule (0.05 probability of a lever press delivering a pellet). After training, 4 matched groups were created: (i) RR20 with injections of saline directly into PPTg, bilaterally; (ii) RR20 with injections of muscimol, a GABA agonist, bilaterally into PPTg in order transiently to inactivate it; (iii) contingency degradation – food pellets delivered regardless of lever pressing; saline injections bilaterally into PPTg; (iv) contingency degradation and muscimol injected into PPTg. Rats received treatments in each of 3 sessions. Contingency degraded rats receiving saline injections into PPTg showed a significant reduction in lever pressing over 3 sessions compared with those not degraded (the contingent group). This reduction in lever pressing did not occur in the muscimol-treated rats. These data show that muscimol injected bilaterally into the PPTg does not impair lever pressing activity, and that a functional PPTg is required to update action–outcome association. Data presented in the PhD thesis of Duncan AA MacLaren, University of St Andrews, 2012.

Fig 1.



'Lesioned rats comprehensively failed and, because there was continual change in food location, pre-lesion training was worthless'

What do these studies tell us? Most clearly, there are no motor or motivational problems: lesioned rats moved freely around the 8ARM, ate food, lever pressed normally and liked amphetamine. Their deficit lies outside these domains.

The data can be accounted for as one of action–outcome association – understanding the relationships between actions and the outcomes produced. In the random foraging task, reward location varied on every trial, so rats had to remember where they had been and not go back – they needed to understand which actions led to which outcomes. Lesioned rats comprehensively failed and, because there was continual change in food location, pre-lesion training was worthless. In the IVSA task, rats were faced with two levers: pressing one did nothing, pressing the other gave drug. Again, lesioned rats could not associate action (correct lever pressing) and outcome (drug delivery) but in this test, if they had previously made an association between lever pressing in the same operant box and reward delivery – by pre-training to press for food – the presence of a bilateral PPTg lesion did not prevent expression of that association. But the progressive ratio schedule beat them – the relationship between action and outcome changed continuously, with more lever presses incrementally required for the next delivery of drug.

Two further things suggest that failure of action–outcome association is a viable hypothesis to explain the deficit: in recent experiments we examined contingency degradation, critical for identifying problems in action–outcome association; and examination of PPTg connections make a role in action–outcome association wholly plausible.

Contingency degradation asks whether, having learned an association, a rat can recognize that contingencies have changed so that they can stop responding. To do this we trained a group of rats on a random ratio–20 (RR20) schedule (0.05 probability of a lever press delivering a pellet; Fig. 1). Once they had all achieved consistent pressing rates we divided them into four groups: contingency degraded or remaining on RR20; with bilateral injections into PPTg of saline or muscimol, a GABA agonist that transiently inactivates it. Rats that were not contingency degraded maintained responding on RR20 regardless of whether they had saline or muscimol injected into PPTg: muscimol did not affect responding. When the contingency was degraded, rats

Fig 2.

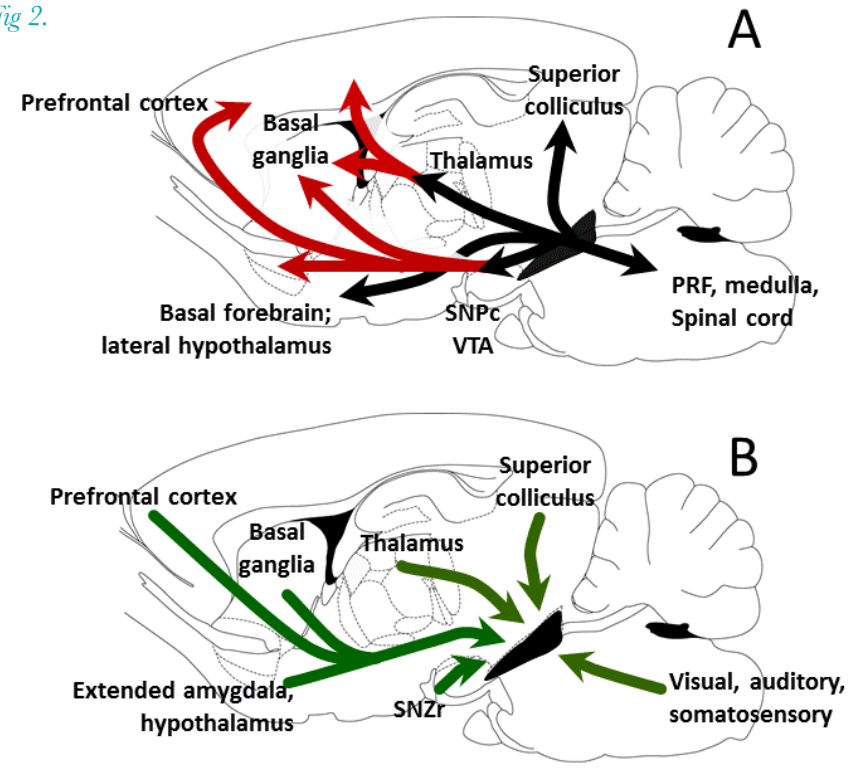


Figure 2. The principal efferent (A) and afferent connections of the PPTg, shown in silhouettes of rat brain (taken from the stereotaxic atlas of Paxinos & Watson). Arrows are indicative only, not direct representations of pathways. A, black lines represent principal efferents: the red lines represent onward transmission through midbrain DA neurons and the thalamus to basal ganglia and cortical systems. B shows – green arrows – the principal areas of brain that project to PPTg. For more detailed reviews of the connections of the PPTg see Maskos (2008), Winn *et al.* (2009) and Wilson *et al.* (2009). Abbreviations: SNPc substantia nigra pars compacta; SNZr substantia nigra zona reticulata; VTA, ventral tegmental area.

receiving saline into PPTg reduced their lever pressing significantly: that is, they updated the action–outcome association, realizing that lever pressing was not delivering food. However, intra-PPTg muscimol led to rats maintaining high levels of lever pressing: there was no updating of the action–outcome association.

This all points to the conclusion that a functioning PPTg – transiently inhibited or permanently lesioned – is critical for forming and updating action–outcome association, a more sophisticated purpose for this level of brain than previously suspected. The anatomical connections of PPTg reinforce this (Fig. 2). Inputs descend from the forebrain – notably from basal ganglia output nuclei – and from sensory structures in midbrain and brainstem. (PPTg neurons show very fast responses to sensory input, especially auditory.) There are dense outputs to the thalamus – all thalamic nuclei have cholinergic input from the mesopontine tegmentum – and to sites of non-specific cortical input, such as the basal forebrain and lateral hypothalamus. Descending connections travel to the pontine reticular formation, medulla and spinal cord (Winn *et al.* 2009).

In the context of action–outcome association, however, the most significant connection is that with midbrain dopamine (DA) neurons (Maskos, 2008). These are known to be critical for learning, and their target sites in the striatum are involved in action–outcome association. Stimulation in the mesopontine tegmentum drives a three-phase release of DA in striatum: a fast spike of DA activity dependent on ventral tegmental area (VTA) nicotinic acetylcholine (ACh) and ionotropic glutamate receptors; decreased activity, mediated by muscarinic receptors at source in the brainstem; and a prolonged increase in DA release, dependent on VTA M5 ACh receptors (Lester *et al.* 2010).

What we suggest is that loss of PPTg input to DA neurons makes action–outcome association impossible because the normal regulation of DA neurons is dysfunctional.

We have argued that, as well as being a basal ganglia input/output station, PPTg also generates rapid responses to novel stimuli independently of forebrain systems (Winn *et al.* 2009; Wilson *et al.* 2009). It is part of a hierarchy of decision-making, operating on very short timescales so that animals can make immediate judgments about the need for action – avoidance of predators or capture of prey, for example.

‘Contingency degradation asks whether, having learned an association, a rat can recognize that contingencies have changed so that they can stop responding’

‘Behavioural control is as important as physiological – animals that do the wrong thing don’t survive – so mechanisms of sensory analysis and decision-making must be represented in evolutionarily conserved older parts of the CNS’

PPTg anatomy is consistent with this: descending connections with motor and autonomic systems; ascending connections with basal ganglia (designed for action selection when there are competing response options); and inhibitory control of PPTg by forebrain systems, to prevent impulsive action. To make immediate judgments, it is critical that PPTg can recognize the significance of events. That it can do so is shown by primate electrophysiological data: one population of PPTg neurons responded proportionately to visual targets predictive of reward delivery and a different population to reward itself (Okada *et al.* 2009). This returns us to original notions of brainstem and its early-evolved functions, but with a critical difference. All vertebrates need to maintain basic physiological processes and control of these is naturally represented in older parts of the brain. But behavioural control is as important as physiological – animals that do the wrong thing don’t survive – so mechanisms of sensory analysis and decision-making must be represented in evolutionarily conserved older parts of the CNS (Wilson *et al.* 2009).

In the effort to understand the neural basis of psychological processing, neuroscience focuses on cerebral cortex and those allo- and sub-cortical structures intimately associated with it. However, because some behavioural decisions have to be made so quickly, key mechanisms of behavioural control must sit further down the neuraxis. What reach might these lower systems have into cognitive processing? It is a question worth asking, because it has been recognized for many years that midbrain DA neurons are involved in cognitive processing and in its disorders. Efforts to treat schizophrenia have focused almost exclusively on regulation of DA receptors in striatum and prefrontal cortex, in the belief that disturbed DA activity is the principal substrate of schizophrenia’s positive signs and symptoms (Frith, 1992). What if the disorder of DA neurons comes from a failure of control by structures that normally supply them with new information, as opposed to descending feedback control? The PPTg is known to be associated with endophenotypic features of schizophrenia, such as failure of prepulse inhibition and control of the auditory P300 as well as increased nicotine use. But more than these, it is conceivable that the catastrophic deficits we see in PPTg-lesioned rats when action–outcome association is needed reflect the problem that schizophrenic patients have in understanding their own and others’ actions – “patients misattribute self-generated actions to an external agent” (Frith, 1992, p.73). It is only speculation, but given the mismatch between the scale of impairment in schizophrenia and the failure to develop viable models of pathology or treatments, it is one worth making.

Critical to this speculation is something that we regard as secure: that brainstem systems have a sophisticated capacity to analyse incoming sensory data, understand that input in terms of what is already known and, if appropriate, make an immediate decision to act. It is the essential process used throughout the brain – analyse input, compare to experience, calculate the most appropriate response. The brainstem is just as brainy as the rest of it, but quicker.

Acknowledgements

I am grateful to many colleagues, including current and recent SIPBS lab members, Morag Farquhar, Nadine Gut, Katarzyna Pawlowicz, Amélie Gavard and Duncan MacLaren. This work has been funded by the Wellcome Trust, BBSRC and MRC.

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Do humans really prolong breath-hold duration by lowering heart rate to reduce metabolic rate?

Humans do not appear to be able to voluntarily lower heart or metabolic rate during breath-holding. So we cannot prolong breath-holds in this way. What might happen when combining breath-holding with immersion remains unclear.

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It is often claimed that humans – and 'elite' free-divers in particular – prolong breath-holding by lowering heart rate to reduce metabolic rate, and even that this might represent a harking back to some ancestral aquatic past. While the scientific literature is never straightforward, it has indicated for many years that this appears to be a myth for breath-holds in resting subjects without immersion.

Over the last decade a number of excellent television programmes about breath-holding have claimed that humans prolong breath-holding by lowering heart rate to reduce metabolic rate. These programmes are great for increasing public awareness and interest in physiology and are useful material for making undergraduate lectures interesting, topical and thought provoking. The accompanying commentaries are excellent, but have the unenviable task of converting complex ideas into a simple and intriguing message. Many viewers just enjoy the visual experience and don't analyse the commentary closely. But if you view the films a number of times the simplifications become more noticeable. The danger of over-simplification threatens when complex physiological processes, which are incompletely studied and understood, have to be simplified to make them exciting for the viewer. Moreover each programme may repeat and so propagate the original simplification. One simplification can be the merging of breath-holds on land (visually dull) with those during immersion (visually thrilling). Another is that humans decrease heart rate during breath-holding to reduce metabolic rate and hence prolong breath-hold duration. It is valuable to highlight some of the classical physiology (Lin, 1982; Lin & Hong, 1996) and original papers indicating that this is a myth for breath-holds at rest and without immersion.

Metabolic rate does not decrease below resting levels during breath-holding

Metabolic rate (the rate of O_2 consumption) is normally measured at the mouth from at least one breath, using an oxygen-filled

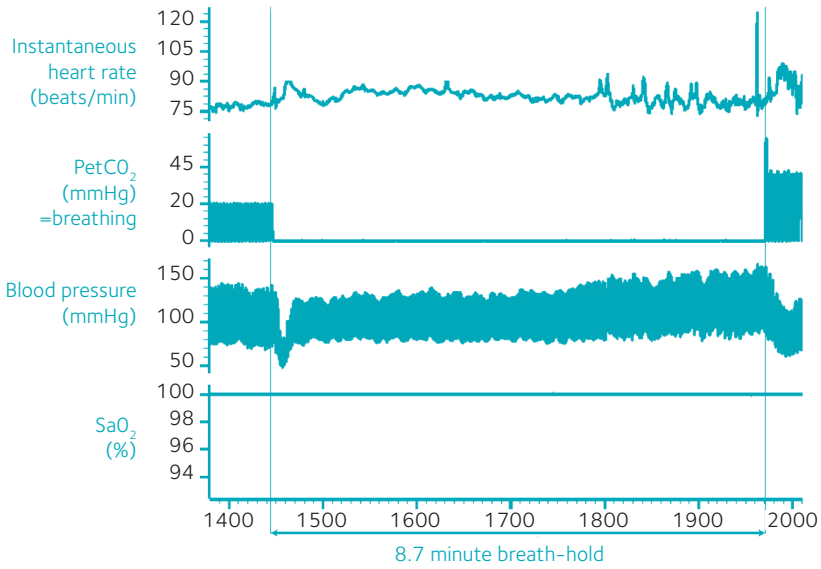

Figure 1. **Little change in blood pressure, heart rate or S_{aO_2} during an ~9 minute breath-hold in a normal subject with preoxygenation and hyperventilation**
Instantaneous heart rate, tidal P_{CO_2} (indicating breathing), blood pressure (Finapres cuff) and oxygen saturation (S_{aO_2}, finger sensor) during breath-holding in one normal subject following preoxygenation, hyperventilation and maximum lung inflation. At breakpoint the peak systolic blood pressure is 162 mmHg and end tidal P_{CO_2} is 55 mmHg.

'Incidentally, the breath-hold duration of 14 minutes Rahn himself achieved with this preoxygenation and hyperventilation represents the most plausible 'longest' breath-hold recorded in the scientific literature'

spirometer or a Douglas bag. Expired air measurements alone are adequate to measure metabolic rate at rest or during exercise, because neither the arterial partial pressure of oxygen (P_{aO_2}) falls nor that of carbon dioxide (P_{aCO_2}) rises. Typical resting metabolic rates are ~250 ml $O_{2,STPD}$ min^{-1}.

Measuring metabolic rate during breath-holding presents more of a technical challenge. Firstly, because it is only averaged over the breath-hold and secondly, because blood gases do deteriorate during breath-holding. So the true metabolic rate can only be measured from the oxygen extracted from both expired air and blood (Hong *et al.* 1971). The key and classic papers are more than 40 years old and so far all have found that metabolic rate in resting humans does not decrease during breath-holding.

In 1946 Stevens *et al.* showed in six healthy subjects that buoyancy gradually decreased during breath-holding. They proposed this was because the oxygen taken up from the gas in the unventilated lungs was not replaced by carbon dioxide gas produced as metabolism continued. Instead, while gaseous oxygen is consumed, carbon dioxide remains dissolved in the blood and tissues (because breath-holding abolishes the partial pressure gradients driving CO_2 from alveolar blood to alveolar gas). The rate of change of buoyancy, i.e. the rate of decrease in lung volume, should correspond to the rate of oxygen consumption measured at the mouth. Stevens confirmed this in three subjects by showing the change in buoyancy was almost exactly equal to the rate of oxygen consumption measured by subjects breathing from an O_2-filled spirometer before and after the breath-hold.

Stevens *et al.* used this to show that the mean rate of oxygen consumption during the entire breath-hold (the rate of change of buoyancy) was ~291 ml $O_{2,STPD}$ min^{-1}, i.e. not below resting levels. (Strictly speaking, they were also immersed, but the water temperature is unknown!) The true rate of oxygen consumption must be higher than this, when also accounting for the additional fall in blood oxygen content during breath-holding. Alternatively, if the lungs are over-filled with oxygen at the start of the breath-hold (i.e. by 'preoxygenating' with

50–100% O_2) and subjects hyperventilate so much that blood gases remain normal even at the breakpoint, oxygen consumption measured only at the mouth produces higher metabolic rate values that should be nearer to the true metabolic rate. Stevens also used breath-holds with preoxygenation (but without hyperventilation) and found that the measured mean rate of oxygen consumption was higher (369 ml $O_{2,STPD}$ min^{-1}). This measure is nearer the true metabolic rate, but still fails to allow for any influences on oxygen carriage of changes in P_{aCO_2}.

In 1959 Klocke & Rahn used spirometers to measure the change in lung volume and its gas composition in six subjects during breath-holds prolonged with preoxygenation and voluntary hyperventilation. They measured no change in the volume of gaseous CO_2 in the lungs during breath-holding (confirming that all metabolically produced CO_2 remains dissolved). They found that the mean rate of decrease in lung volume corresponded to 300 ml $O_{2,STPD}$ min^{-1}. Incidentally, the breath-hold duration of 14 minutes Rahn himself achieved with this preoxygenation and hyperventilation represents the most plausible 'longest' breath-hold recorded in the scientific literature (although anecdotes exist of even longer holds).

Finally, in 1971, Hong *et al.* attempted to derive the true rate of oxygen consumption for an entire breath-hold (but only in 2 subjects) when combining spirometry with blood gas sampling and found a mean metabolic rate of 212 ml $O_{2,STPD}$ min^{-1}. Note the usual paradox in the physiology literature of there being so much variation between studies that the 'true' 1971 value from only 2 subjects is lower than the underestimates from the 12 subjects in 1946 and 1951!

A definitive study of validated measurements of true metabolic rate before and during breath-holding using a larger number of normal subjects would be welcome. Nevertheless, the available evidence indicates that metabolic rate does not decrease below resting levels during such breath-holds.

'Mean' heart rate remains above 55 beats min^{-1} during breath-holding

Heart rate is so easy to record during breath-holding that it is often reported, in case it might be important. There are, however, three difficulties with breath-hold studies. First, the heart rate change depends on the gases inhaled at the start of the breath-hold (heart rate does not fall when breath-holding with preoxygenation). Secondly, baseline heart rate rises in anticipation of breath-holding (especially if voluntary hyperventilation occurs) which will exaggerate subsequent 'falls'. Thirdly, the presence of respiratory sinus arrhythmia (Cooper *et al.* 2003) before and during (showing that voluntary breath-holding cannot stop the central rhythm (Parkes, 2006) complicates establishing the precise heart rate changes with breath-holding.

In the best review of heart rate changes with breath-holding, Lin (1982, his Fig. 2) reports pre-breath-hold heart rates of 65–100 beats min^{-1} and that during breath-holding 'mean' heart rate always remains above 55 beats min^{-1}. Counting the total number of

‘A definitive study of validated measurements of true metabolic rate before and during breath-holding using a larger number of normal subjects would be welcome. Nevertheless, the available evidence indicates that metabolic rate does not decrease below resting levels during such breath-holds’

heart beats during the breath-hold gives a more realistic indication of its metabolic demands (so it is better to compare mean heart rate with metabolic rate, which is itself always measured as a mean over the entire breath-hold). The overall heart rate change vs. pre (not resting conditions) therefore reported was sometimes a rise, no change or a slight fall. Subsequent literature still supports this conclusion. Furthermore, we know that in most studies measuring cardiac output during such breath-holds, it is still ~6 l blood min^{-1}.

Anecdotally, the lowest minimum heart rate value during breath-holding in individuals is ~30 beats min^{-1} in two subjects (Ferrigno *et al.* 1991, their Fig. 4). On the other hand anecdotally, the most striking example of where a heart rate fall might be expected but is not observed is during prolonged breath-holds (using preoxygenation and hyperventilation). Figure 1 shows a recent ~9 minute breath-hold in my laboratory where respiratory sinus arrhythmia persists and instantaneous heart rate never falls.

How far must heart rate fall to reduce metabolic rate?

Obviously the heart’s beating consumes oxygen. So any decrease in heart rate not accompanied by an increase in stroke volume will consume less oxygen. But the human heart (with a mean weight of only 300 g) typically consumes only ~35 ml $O_{2,STPD}$ min^{-1} at rest (Takaoka *et al.* 1992). In other words, even if the heart stopped beating altogether, this would reduce resting metabolic rate by only ~14%. So for resting humans breath-holding without immersion, even a large decrease in mean heart rate will cause only a small reduction in overall metabolic rate.

The available evidence therefore shows that ‘mean’ heart rate does not fall sufficiently to produce measurable decreases in metabolic rate. And anyway during such breath-holds metabolic rate does not measurably decrease!

Conclusions

None of the scientific literature I can find demonstrates that ‘elite’ breath-hold divers have any unique abilities to reduce both mean heart and metabolic rate during breath-holding at rest and without immersion. So the current scientific literature exposes some of the mythology around breath-holding.

What might happen during immersion, especially in freezing water is, however, another story. The additional variables with immersion (how reliable are ECG measurements underwater? what duration? what depth? what water temperature? how hard were they swimming?) make this an even more complex question to unravel.

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Q&A: Remembering Sir Andrew Huxley

Sir Andrew Huxley, 'the most eminent physiologist of a generation', passed away in May this year. We asked some Members who knew him to share some of their memories of the man who unravelled the propagation of the action potential and unveiled the sliding filament mechanism in striated muscle.

Virginia Huxley

Professor of Medical Pharmacology and Physiology, University of Missouri-Columbia Medical School

How close were you to your uncle, Sir Andrew Huxley?

The first time I recall meeting Uncle Andrew was when he took his family on a tour of the States after he got the Nobel. He was a very out-going person who was able to engage with children. Shall we say that was in stark contrast with his older brother, my father [David Huxley]. They were close as children, but they diverged at about university time. After the War, he and my mother ended up in Bermuda, where Daddy was attorney general, then solicitor general, and then acting governor. What's sad is that my father always felt he was a failure by comparison to Uncle Andrew. It's like, good grief, Daddy!

My mother was American and she thought that it was a lot of stress on the children to grow up with the Huxley moniker. So she decided to remove us from that as much as possible.

We started to have more contact with Uncle Andrew (1963 with my eldest sister's wedding and we came over to the UK) because two of my sisters ended up in England. One married a Darwin and the other married another Huxley!

Was he helpful in your career?

If Uncle Andrew was following my career, I wasn't aware of it back then (as a student). But he was one of those people who could scare the bejesus out of you because he just absorbed everything that was going on around him.

I gave my father a copy of my [PhD] dissertation – a study on oxygen diffusion boundary layers (in fact, it was my first paper in *The Journal of Physiology*!). I was in this programme that I thought was original and that no one else was doing, called 'biophysics' (at the University of Virginia). So the dissertation was in the library in the house my father retired to – which was actually where my grandmother was living, so Andrew was over there quite frequently. Apparently he just picked it up and removed it. And I know this because I received a four-page, carefully penned critique of it. I was totally floored, because his reading of my dissertation was, frankly, better than anything that any of my dissertation committee members had done.

That's when it really struck me that he wasn't just a neurophysiologist or a muscle physiologist, but that, well, yes, he's sort of considered to be one of the founders of biophysics! This area that I had thought was pristine! After I'd begun to put two and two together, I went and did a critical read of, well, most of his papers. All I could do was just laugh because I realised that I had backed right into it. Where I was intellectually comfortable were areas that he had already ploughed. For me the science is the intellectual pursuit and the joy of that. What I realised in looking at his work is that's exactly what the driver was for him.

He always stood to the side. But I realise that he also took interest in what I was doing. In '87 he and Aunt Richenda came out to Columbia and spent some time here with me. What was great was he was now visiting my lab and my setup. What I study is exchange in the microvasculature, and I do a number of studies that are *in vivo* – from a biophysicist standpoint – I try to control the various components. And it's the old problem of how do you study a living system without disturbing this system just by studying it. So we've developed a number of techniques that really are not standard to try to do this. We

had a great day with him in the lab on his hands and knees under my microscope rigs. It was hysterical: I kept thinking, "There's Sir Andrew Huxley, crawling on the floor, having a great day!"

I realised that most people either wouldn't have that conversation with Sir Andrew, because they'd think he was looking for something else or that he was going to ask some penetrating question that was going to kill them, or God knows what. In his quiet, he could be intimidating.

My first presentation to The Physiological Society was actually at St Thomas'. A December meeting. I was talking on some work that I was doing as a postdoctoral fellow at the University of California. In the audience was Uncle Andrew. At that point he was President of the Royal Society. At that point he wore half-glasses that would go about mid-way down the bridge of his nose, and he and my father both had eyebrows that you could land a pigeon on! When they would look up at you, over the half-glasses and under the eyebrows, you felt as if you were being seared with laser light. I have never been so goddamn nervous in my entire existence! Knowing that it was going to be voted on and that stuff, and that they were scrutinising 'Sir Andrew's niece', and thinking "Thank you, Mummy, that I wasn't brought up with this!" The relief was incredible when it was accepted.

That evening at dinner, Andrew asked if I would join him at high table, and at the end of the evening – these are tiny little things, but huge – Uncle Andrew said would I like it if he found me a cab, and I said "That would be lovely!" So he hailed a cab and as I'm getting in he said, "Should you like to become a Member of The Society, I'd be pleased to put you forward," as he shut the door.

I almost fainted. It wasn't "You did a good job, I'm proud of you," it was "I wouldn't be embarrassed to put you forward as a Member".

Mind you, the next time I gave a talk, the talk finishes and "Are there any questions?" Uncle Andrew pipes up and asks this question. This is where an American upbringing can get you into trouble; I hear myself saying "Uncle Andrew, you asked me that question a few years ago and the answer remains the same." And a part of my brain is going, "Jesus Christ! What are you doing?!" There was this audible gasp from the audience. I thought I was going to just die! As I raised my head up I realised he was just grinning! I mean, again, everybody else would have had to have turned and looked to see what I saw, but they were just appalled at this brash American! And I realised that I was slipping into a familiarity, like, "Oops!"

What personal qualities led to his achievements and great standing?

Part of it was the powers of observation and the other one – which I think is disappearing from science – the power of sitting back and watching and thinking about things.

Another one is how to be intuitive and follow through on that. It's almost like everybody at the moment wants things to be formulaic: A leads to B leads to C. The thing that's so beautiful about physiology is that it's not linear. To solve the problem you have to allow your brain to take some unusual steps. The power that he had, was he could do that and then back-fill. He could then lead people from A to B to C. He took the time to observe it, think about it, figure out how to test it. It's like, guys, get back to joy of the science!

Is there something about him that people may not know?

He only made it 94.5% of the way to his age goal! Granny lived to 104. His target was just to be a centenarian.

IUPS Congress, Helsinki, 1989. Left to right: Joseph Meyer, Sir Andrew, Ingrid Sarelius, Gabriella Piazzesi, Virginia Huxley, Vincenzo Lombardi

Bob Simmons

Emeritus Professor of Biophysics, King's College London

'Prof', as I knew him, was about 50 when I became a postdoctoral fellow in his laboratory at UCL in 1968. I found him, in all senses of the word, awesome. He seemed to know everything and to be able to do anything and in spades: applied mathematics, physics, engineering, material science, electronics, mechanical skills, an encyclopaedic knowledge of quantitative physiology, great insight, great intuition.

He was human though. I noticed a few endearing pet hates: transistors ("I gave up designing circuits when valves went out"), biophysics as a subject ("It's just the interesting bits of physiology"), statistics ("It's only a bad experiment that needs statistics"), and there was a certain reserve about chemistry and computers. There was a diffidence about protein structure and I think his intuition failed him here. He hated the phrase 'conformational change', saying of the word 'conformational' that it had the same import as 'bloody'; all it signified now was that a noun would follow.

He was very much a modeller; he would think of the simplest model that would make a biological phenomenon tractable, sometimes rather Meccano-like, and then work it out mathematically. He often said that in biological models the difficulty wasn't the mathematics, it was formulating the question. He was an extraordinary problem-solver; whenever we hit a non-trivial technical difficulty he would just stand there and think, sometimes for half an hour, until the solution came; only rarely would he say, "I need to do this on a piece of paper." I often wondered whether he was writing on his mind, as it were, or if he was summoning up some supra-sensory occult power. I didn't like to ask.

He was in some ways a hard task master. I can't remember him ever explaining anything to me, like a mathematical derivation or an idea, in any detail. He expected you to work things out for yourself, get up to speed, and only then would he discuss the problem, and on equal terms. You came to expect robust criticism and, if it came to an argument, he was brilliant and forceful. It was hard to win even when you knew he was wrong. But, in spite of all that brilliance, when I think of him now, what I chiefly remember is how kind he was.

Martin McDonagh

Honorary Senior Research Fellow, University of Birmingham

I was a MSc student at UCL in the mid 1970s and I had gone into the Kardoma coffee bar on Tottenham Court Road for a bite to eat. To my astonishment, there, alone with a cup of coffee, sat Andrew Huxley, Nobel Laureate and Royal Society Professor. We had just had a series of lectures from him on the action potential, so I summoned up my courage and introduced myself. I was surprised to find him very affable and so I talked to him about the project I was struggling with at the time. He was full of good suggestions and I was so intoxicated by the encounter that I left the Kardoma without paying, only to be pursued by the waiter.

"I thought I should have to pay for you and collect it from you in the morning!" he joked in a most friendly manner. With a hot face, I paid up and made a fast exit.

Huxley was held in great awe in the department and even some senior professors were frightened to speak to him. "He relaxes by reading Russian scientific papers – in the original Russian," was one of the departmental jests. You can therefore imagine why consternation greeted me when I arrived late at the lab the next morning.

"Where on earth have you been? Professor Huxley has been asking for you! Go up to his office at once!"

I think the lab thought I must at least have murdered somebody to receive such a summons from Olympus! I climbed the staircase with much trepidation and gingerly knocked on his door.

"Come in, come in! I've been thinking about your project and I have asked a chap from the Hammersmith to contact you. He is doing something rather similar and should be able to help you."

From that day on he always had a friendly word for me in the corridor and my fellow postgraduates just could not understand what special magic power I had to be on such friendly terms with Zeus. Of course, the Hammersmith contact did get in touch – and quickly!

Thereafter, at Society meetings, Professor Huxley vaguely or clearly remembered me – I could never discern which. However, much later when I had my own postgraduate, 'the Kardoma incident' ensured that I had no fears about suggesting that he should speak to Huxley about problems with his apparatus and later about post-doctorate opportunities in the USA.

Elba Island, Italy. Left to right: Vincenzo Lombardi, Sir Andrew and Yale Goldman

Yale Goldman

Professor of Physiology,
University of Pennsylvania

How did you come to know Sir Andrew?

I did a post-doctoral fellowship under Bob Simmons in London, in Huxley's lab at the UCL, from Fall '75 to the beginning of 1980.

Yes, I was intimidated by coming to work in his lab. I wouldn't say everyone would call him approachable, but I got along with him quite well. He was very nice to me and very interested in my science. I think he liked talking to me, so he made it easier for me.

What was he like to work with?

Around the winter holidays at the end of 1980, I had built this new way of looking at muscle fibre striations using white light optical diffraction. This is something that had come up in conversation with Huxley while I was in London. So I was building this setup in Philadelphia that he had helped to suggest and design. He was going to come and visit just after the holiday, in January. I basically just lived in that lab through the winter vacation, trying to get it ready so I could show Prof Huxley that the idea worked. We did get it working well enough to demonstrate the principle, but there was something in the optics that was confusing me horribly. It had to do with beams of light coming through the muscle fibre. At one point it got very blurry. I knew a bit of optics myself, but still I couldn't figure out why it was getting blurry at that one point. I was trying everything. It wasn't a matter of focus or positioning or things like that.

So, Huxley came and we showed him that the thing worked, which was great. Then I said, "Prof, do you have any idea about this bit here where it's going blurry?"

He stared at it a little while. He took a filter paper and put it in the beam so he could see what was happening with the optics. He thought about it for a second. Then he took this one lens – a big aspherical lens, two inches in diameter – and he pulled it out of the set-up and he flipped it around 180 degrees, so that the light was going through it in the other direction.

That fixed it! He figured out, just from his short interaction with this thing, that I had the light going through the lens in the wrong direction. That's not something that you usually think about. There and then he fixed the problem I'd been fretting over all that time!

What personal qualities led to his achievements and great standing?

He was fascinated with all sorts of science, and was so knowledgeable about all kinds of topics that you could engage him on practically any scientific or social issue. His overall range of knowledge was amazing. He had opinions on all of it. It was really fascinating to talk to him.

What might people not know about Sir Andrew?

I remember him talking about what happened during World War II when he was in the military. He told my wife and I – he was talking about just a few days before the invasion of Normandy – that for some reason they went on a boat and they crossed the channel and were walking around on the beaches in France. I don't know if you'd call it spying, but certainly looking over the situation.

It was, of course, occupied by Germany at the time. I asked, "Wasn't it dangerous?!"

He said, "No!... Well, yes, maybe it was, but anyway, we were there!" He just had this very calm attitude towards the whole thing. Perhaps the details, such as the timing, have become distorted.

I don't remember him ever bringing the subject up except that one time.

Left to right: Prem Kumar, Ian McGrath, Colin Blakemore, Sir Andrew, Mike Collis, Graham McGeown, Denis Noble and Dafydd Walters

Mike Collis

Physiology News Editor

In November of 2007 I organised a dinner in London for Sir Andrew Huxley to celebrate his 90th birthday. Other guests included the executive committee of The Society and past presidents Denis Noble, Colin Blakemore and Dafydd Walters. A very good dinner was enjoyed by all. But before the cheese was served, Sir Andrew said he must leave as he wanted to be in good form for the symposium that was being held in his honour at UCL the following day.

I escorted him downstairs from the dining room and called a taxi to take him to The Royal Society, where he was staying that night.

"Would you like me to accompany you in the taxi?" I enquired.

"No, no, not necessary," he replied, "I can find my own way."

I returned to the dining room and enjoyed the rest of the meal and settled the bill. The rest of the guests were preparing to leave, but Colin Blakemore couldn't find his coat. A similar coat was found, but it belonged to Sir Andrew, not to Colin. Sir Andrew must have picked up the wrong coat!

A quick inspection of the coat revealed a return ticket to Cambridge and a book. Ian McGrath volunteered to call into The Royal Society the next day to exchange the coats and the party broke up in good spirits.

The following morning I arrived at The Society office as usual, only to receive a phone call from a worried Ian McGrath. Sir Andrew had not been seen at The Royal Society. My heart sank – what had happened? And was I responsible for losing the most eminent physiologist of a generation?

Before contacting the police or the hospitals, I phoned Carol Huxley – his daughter-in-law in The Society publications office in Cambridge. "Carol, I don`t want to worry you, but Sir Andrew didn't arrive at The Royal Society last night and we don`t know where he is!"

"Oh, don't worry," replied Carol "He is on the train back to London to attend the symposium at the UCL. And by the way, he said he wants his coat back!"

David Trentham thanks Sir Andrew following his talk at a symposium marking his 90th birthday in November 2007

David Trentham

Honorary Professor, The Randall Division of Cell and Molecular Biophysics, King's College London

I first met Sir Andrew in 1972, as a young independent investigator, at the 37th Cold Spring Harbor Symposium on Quantitative Biology. A question from Andrew followed my talk. When just about ready to respond, Annemarie Weber, already distinguished for her discovery of the role of calcium in muscle, leant across to Bob Davies and whispered "The hounds have got him!"

So began my first exchange with Andrew. Afterwards we had a conversation that had enormous impact on my whole thinking about the role and mechanism of the myosin ATPase.

I was privileged over the next three years that my papers to the *Biochemical Journal*, with Clive Bagshaw, were read by Andrew and by Hugh Huxley prior to submission for publication. Their comments and insights, especially from a broader perspective, were invaluable.

My principal opportunities for meeting Andrew in the years that followed were at scientific conferences, especially the triennial Gordon Conference and Alpach meetings on muscle. For 20 years through the seventies and eighties, the climax of these conferences was the summary session on the last day when Andrew put into perspective all that we had learnt at the conference and what was new.

In his later years I was able to visit Andrew occasionally in his lovely home in Grantchester to be greeted with warm hospitality by him and his eldest daughter, Janet. Often, Scottish pancakes with raspberry jam were served, reflecting perhaps his love of Scotland's west coast.

One of his last major meetings was the celebration of his 90th birthday at University College London. It was a memorable occasion in which respect and affection for Andrew were so much in abundance.

Jonathan Coles

Research Associate (Infection Immunity and Inflammation Medicine), Institute of Infection, Immunity and Inflammation, University of Glasgow

Andrew Huxley was notable for his relentless scientific enquiry, his conscientiousness, his courtesy and his great generosity. My contact with him was mainly confined to 1967-1971 (he supervised a long, drawn-out MSc project), but the memories are vivid. He very generously let me use his personal lathe, his personal microscope, and a Cooke objective that he had had modified so that the front surface was concave spherical and it could be immersed in a medium of any refractive index.

At one point, he suddenly had the idea that an aperture from an electron microscope might be useful for the optical system. He did not wait until the next time he saw his young student to suggest that he look for one, instead, he went to the microscope room on an upper floor – presumably bounding up the old wooden staircase – got a couple, came down, burst into my lab and presented them to me with the modest suggestion that they might be worth trying.

Ann Silver

Physiological Laboratory, Cambridge

Many people will have thoughts about Andrew that extend beyond his enormous contribution to physiology. I, for one, will always remember the alarming way he used to come down the stairs in the Cambridge Physiological Laboratory two at a time – a characteristic he exhibited well into old age.

Andrew was one of the minority of Fellows of The Royal Society who were active in supporting animal experiments. While Andrew was, by his own admission, quite shy, Richenda, his wife, was not. At the 1993 IUPS Meeting in Glasgow she wore a t-shirt emblazoned across the chest with 'I support Animal Experiments'. Many others chose to display the same wording on a small metal badge, but that made far less impact!

At Andrew's Funeral Service in Trinity College, Cambridge, in June this year, his son, Stewart, recalled energetic family holidays on the west coast of Scotland. He also mentioned Andrew's early War work (before he became involved in operational research in gunnery) when he was part of a small group who, laden with heavy rucksacks, walked for miles every day assessing nutritional requirements. Perhaps these experiences contributed to his stamina.

Visit www.physoc.org/sir-andrew-huxley for more memories, photos and video of Sir Andrew Huxley.

Reps' meeting, Physiology 2012

Outreach Manager, **Louise Crane,** reports on the meeting of The Society's university Representatives

Society Representatives play an invaluable role in promoting The Physiological Society's activities to both current and prospective Members. There are 78 Representatives at universities throughout the UK and abroad – in countries such as Qatar, Nigeria and Ukraine. These 'Reps' act as a conduit between The Society and our Members, providing a point of contact for both Society staff and our network of physiologists worldwide.

Reps can also provide feedback to The Society, to help us provide a better service to you. What schemes are working well to support Members? How can we attract more physiologists, neuroscientists, biomedical scientists, etc. to The Society?

These questions were discussed at the Reps meeting at Physiology 2012 in Edinburgh this July. Sixteen of our Reps came together with Louise Crane, Outreach Manager, and Michelle Brook, Policy Manager, to review the schemes and roles Reps are responsible for, with a focus on how to promote The Society within their institutions.

Before the main discussion, Louise and Michelle reviewed the activities of The Society since the last meeting of Reps in September 2011. The schemes that Reps co-ordinate were then discussed, including: the Vacation Studentship Scheme; the Undergraduate Prize; and the Departmental Seminar Scheme. All these schemes are overseen by the Education and Outreach Committee, who will review them based on the Reps' input in September.

One suggestion was that winners of the Undergraduate Prize should be publicised more: on university websites, on social media and in local newspapers. This suggestion can apply to all achievements of Society Members – any prizes won or activities undertaken could be announced to a wider audience.

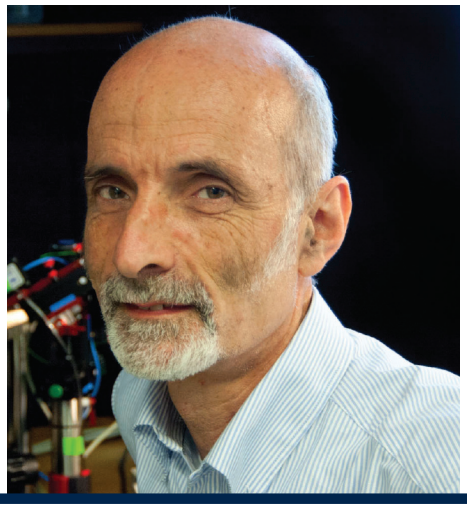
Lucy Donaldson, Society Representative at the University of Bristol, recruited 124 undergraduate Members this academic year. She offered particular insights into attracting young physiologists to The Society. Bristol is in the fortunate position of having a physiology and pharmacology department, which provide funding to cover the £10 membership fee for all undergraduates. This is not the sole key to recruitment, however. Reaching out to students personally works – face-to-face communication is much more powerful than electronic – and so asking students to join at a meeting, seminar or lecture is very effective.

The following new Society Representatives were given special mention at the meeting:

- Anthony Lewis, University of Portsmouth
- Claire Peppiat-Wildman, Royal Veterinary College
- David Mazzocchi-Jones, Keele University
- Jane Haley, University of Edinburgh
- Mala Shah, London School of Pharmacy
- Matt Mason, University of Cambridge
- Neil Morris, University of Leeds
- Richard Mackenzie, University of Westminster
- Rita Jabr, University of Surrey
- Scott Wildman, Medway School of Pharmacy

We are always looking for new Society Representatives at institutions that don't already have one. In recognition of the work, Reps receive free membership during their tenure. If you would like to become a Society Rep, please email societyreps@physoc.org.

My top ten papers



Jonathan Ashmore reflects on the papers that have most influenced his career

I started my scientific career as a theoretical physicist. That phase didn't last long. Real hands-on lab work was easily much more fun. This history explains the first 2.5 papers. There is naturally a biophysical slant to the others, although I would have liked to have included many more. Disloyally, some of the later papers are not taken from *J Physiol*, a trend in neuroscience which I hope *The Journal* can reverse.

1

Dyson FJ (1949). The S matrix in quantum electrodynamics. *Phys Rev* **75**, 1736–1755.

As theoretical physics graduate students, we actually read alarmingly few papers: the information came through precirculated 'preprints' appearing often years before the journal version. But this paper we read for inspiration: it outlines a programme of how to remove annoying infinities in the calculations (the denominator was often 0!) from an otherwise beautiful theory. The problem of renormalization is still with us in the post-Higgs world, but this was my introduction to a complex edifice where, as in physiology, the devil is in the detail.

2

Marr DA (1969). Theory of cerebellar cortex. *J Physiol* **202**, 437–470.

This paper, written by David Marr when he was still a PhD student with Giles Brindley, combines an elegant theoretical idea about how to extract complex patterns from an even more elegant structure, the cerebellum, and form a wide range of complex motor responses. As a theory paper it had a remarkable impact just at the moment when LTP was just about to be discovered.

3

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.

Published exactly 60 years ago, this paper is still just as fresh today as it was then. But, encountered with the mindset of another discipline the description is hard to stomach – where do the ideas come from? It is really a 'phenomenological' model (i.e. an informed way of fitting data), but with a long tradition of physiology. The effort to compute the correct action potential velocity, all done by Andrew Huxley using just a hand-cranked Brunsviga calculator, today makes the blood run cold.

4

Fatt P & Katz B (1952). Spontaneous subthreshold activity at motor nerve endings. *J Physiol* **117**, 109–128.

1952 must count as an annus mirabilis of *The Journal*. This paper describes the discovery ('a chance observation') of miniature endplate potentials in the early intracellular recordings with microelectrodes. It expresses all the excitement of finding something completely new and the possible explanations are discussed with an incisive logic. With hindsight, many of the observations, (for example, that the frequency but not the amplitude of the minis is calcium-dependent), is the foundation of much subsequent synaptic physiology.

5

Hamill OP, Marty A, Neher E, Sakmann B & Sigworth FJ (1981). Improved patch-clamp techniques for high-resolution current recording from cells and cell-free membrane patches. *Pflugers Arch* **391**, 85-100.

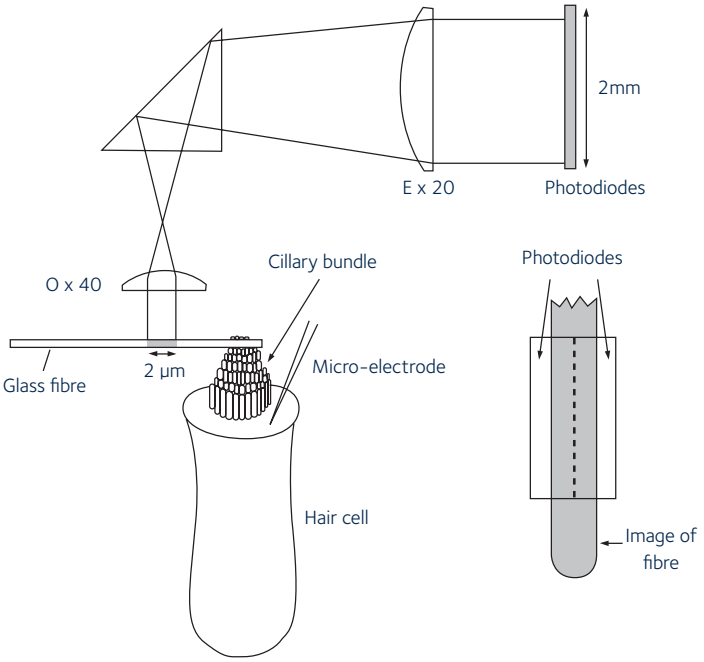
This is the methods paper par-excellence. It let patch-clamping become one of the key enabling technologies of neuroscience. It has often (maliciously) been said that, had patch-clamping been discovered in a molecular biology lab, we would still not know how to do it!

6

Corey DP & Hudspeth AJ (1979). Response latency of vertebrate hair cells. *Biophys J* **26**, 499–506.

This paper firmly established the notion that hair cell transduction is 'direct'. A chemical signal between bending the stereocilia and the opening of the ionic channel was a hypothesis which until then was at least plausible given what was then known about photoreceptors. It opened up the problem of identifying the molecular basis of sound transduction. The question is still un-answered.

The original method to measure hair bundle movement with a flexible fibre and photosensor. Widely copied and used to this day. From Crawford & Fettiplace, 1985. *J Physiol* 364, 359–379.



7

Crawford AC & Fettiplace R (1985). The mechanical properties of ciliary bundles of turtle cochlear hair cells. *J Physiol* **364**, 359–379.

The first convincing observations of 'active' processes in hearing. The experiments describe nanometre movements in hair bundles, but in non-mammalian hearing organs. These results spawned a whole research field which is still thriving today and fuelled the debate about what amplifies sound in the mammal (which is categorically not, in my view, the hair bundle!).

8

Hilgemann DW (1994). Channel-like function of the Na^+,K^+ pump probed at microsecond resolution in giant membrane patches. *Science* **263**, 1429–1432.

This is another technically inspirational paper. Don Hilgemann rebuilt an Axon amplifier to record ultrafast events in membrane biophysics, the transition of ions into the sodium pump. Not only that, it addressed the perennial problem of how to isolate very small amounts of the pump in membranes. I like this paper because it has a definite 'wow!' factor.

9

Zheng J, Shen W, He DZ, Long KB, Madison LD & Dallos P (2000). Prestin is the motor protein of cochlear outer hair cells. *Nature* **405**, 149–155.

This paper identified the key motor molecule that makes outer hair cells move. Jing Zheng, as a side-project in Peter Dallos's lab, had been collecting enough inner and outer hair cells over 12 months (by aspirating single cells), to make a cDNA subtraction library. Although the paper does contain a suspect calibration, the effect on the field of identifying the molecule was profound. We have yet to work out prestin's structure.

10

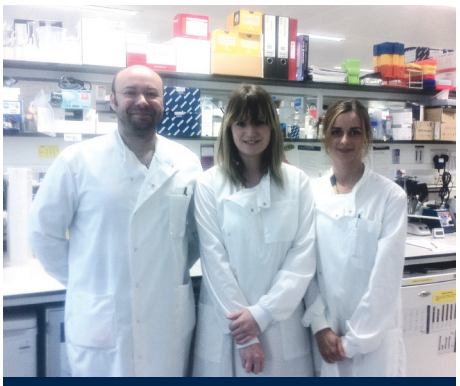
Goutman JD & Glowatzki E (2007). Time course and calcium dependence of transmitter release at a single ribbon synapse. *Proc Natl Acad Sci U S A* **104**, 16341–16346.

This paper describes experiments where both presynaptic and the (extremely small) postsynaptic bouton of the hair cell afferent dendrite were simultaneously patch-clamped. It demonstrates convincingly the hair trigger release of glutamatergic vesicles, probably as multi-vesicular events, at the ribbon synapse. Not only is it a technical tour-de-force (it describes those experiments that only work once every month) but it describes the results with impeccable economy.

It might be said that I have chosen too many 'old' papers. To which I reply that these papers were indeed formative – they have a fine balance of numeracy and description – and, even now, on re-reading them, I think that they have stood the test of time well as models of how to present good and exciting science.

Lab profile: The Biomedical Research Centre, University of East Anglia

Louise Cully, PhD student, on a lab 'in its infancy', benefiting from being located within the Norwich Research Park



Left to right: Giles Watts, Louise Cully and Milka Budnik-Zawilska

The Univeristy of East Anglia Biomedical Research Centre (BMRC), in which I have been working as a PhD research student since last October, is an integral component of the Norwich Research Park (NRP). The NRP is a collaborative partnership between the University of East Anglia, the Norwich and Norfolk University Hospital, and four independent, world-renowned institutes of research: The John Innes Centre, which focuses primarily on plant genetics and microbiology; The Institute of Food Research; The Genome Analysis Centre; and The Sainsbury Laboratory. Unique multidisciplinary research is made possible through close cooperation between many of the individual research centres located within the NRP's 160 hectares.

The BMRC is home to over 100 scientists in numerous research groups undertaking pioneering work into arthritis, cancer, cardiovascular and neurological disorders, diabetes and infectious diseases. The BMRC's Disease Modelling Unit allows transgenic, knock-in and knock-out model systems to be utilised in investigative research, encouraging interdisciplinary coordination from molecular biology up to whole-system physiology.

In 2009, my primary supervisor, Giles Watts, who is currently a lecturer in cell biology and biochemistry within the Faculty of Health, relocated to Norwich following a position as Instructor in Paediatrics and Medicine at the Children's Hospital in Boston, Massachusetts. His research is conducted around the autosomal-dominantly inherited multisystem disorder Inclusion Body Myopathy associated with Paget's disease of Bone and Fronto-temporal Dementia (IBMPFD; OMIM to #167320). In 2004, using a candidate gene approach, he identified mutations in valosin-containing protein (VCP) as the causative factor in the pathological development of IBMPFD. It was after this discovery that his area of interest shifted towards the elucidation of the physiological role of normal and genetically mutated VCP in biological tissues; mainly bone, muscle and brain – the three primary tissues affected by VCP mutation.

VCP is a ubiquitously expressed member of the AAA+ (ATPase associated with diverse cellular processes) protein family, with multifarious functions in the ubiquitin–proteasome system (UPS) and retro-translocation of endoplasmic reticulum-associated degradation (ERAD) substrates. VCP binds various combinations of primary and secondary co-factors to form a molecular chaperone complex, shuttling misfolded cytosolic protein aggregates to the proteasome. When a loss-of-function mutant VCP is expressed, cytosolic and nuclear accumulation of aggregated, ubiquitinated proteins is observed. The presence of these 'inclusion bodies' and rimmed vacuoles in brain and muscle tissue are some of the diagnostic markers of IBMPFD. The muscle pathology – my own area of research – is accompanied by muscle fibre degeneration, rimmed vacuole formation and ubiquitin-containing sarcoplasmic inclusions. Moreover, muscle fibres of $VCP^{R155H/+}$ knock-in mice display severely swollen and abnormal mitochondria, suggesting that they may have impaired energy metabolism.

Since joining the Watts lab, my work has been focused on analysing the functional effects of mutant VCP transfection into stable cell lines. To date I have used plasmid expression vectors carrying VCP R155H and A232E mutations in cultured HeLa cells in order to determine the effects of VCP mutant expression on mitochondria dynamics and metabolism. Over the last few years, work on PINK1 and Parkin have highlighted the importance of the UPS in regulating the biogenesis and clearance of dysfunctional mitochondria as part of cellular homeostasis. Since VCP in an integral part of the UPS we believe it is involved in mitochondrial protein 'quality control'.

My research also involves assessing the physiological and functional effects of VCP mutation in skeletal muscle using a murine $VCP^{R155H/+}$ model. Under the guidance of my secondary supervisor, Gabriel Mutungi, I am assessing the fatigue characteristics of the extensor digitorum longus and soleus muscles, which consist of mainly type IIb/x fibres and type I and IIa, respectively. This allows us to characterise the fibre type-specific properties of the mutant mice in the context of ageing.

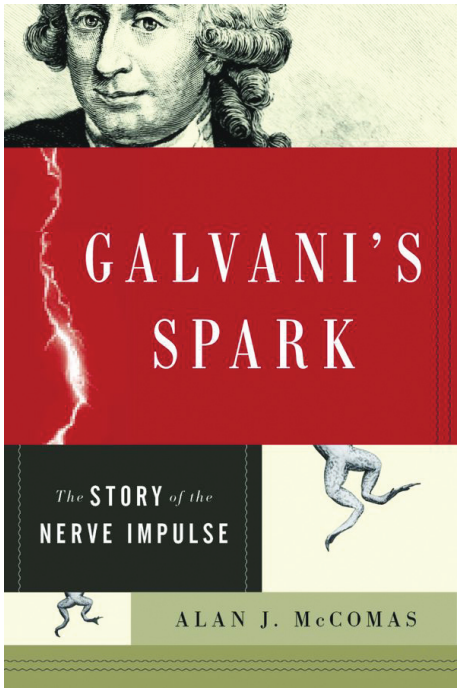
My colleague, Milka Budnik-Zawilska, a second-year PhD research student in the Watts lab, is investigating the role of VCP in the autophagic pathway. As Paget's disease of bone is one of the pathologies of VCP mutation, Milka's work involves determining the mechanism by which VCP mutations result in irregular and disorganised bone remodelling, a hallmark feature of PDB due to excessive osteoclast activity. Pagetic osteoclasts are excessively large, multinucleated and contain VCP-, p62- and ubiquitin-positive inclusion bodies, implying a homeostatic role for VCP in the regulation of osteoclast activity in the disease-free state.

While our lab is still in its infancy, we are exceptionally lucky to be part of the BMRC and to work alongside many knowledgeable research scientists with varying areas of expertise, allowing for integration, collaboration and the continuation of high standards of scientific research.

Book review: Galvani's Spark by Alan J McComas

Angus Brown

Associate Professor of Neuroscience, University of Nottingham



Oxford University Press
ISBN-10: 0199751757
ISBN-13: 978-0199751754

In a previous review (PN 84, 2011) I pleaded for a book entitled 'A History of Twentieth Century Electrophysiology' and my prayers have been answered! In this book, McComas describes the evolution of our knowledge of the nerve impulse from the serendipitous discoveries of Galvani over two centuries ago, to the present day. The story starts with detailed descriptions of Galvani's discoveries around the frog peripheral nerve and his feud with Volta, who claimed that the electricity required to generate the famous muscle twitches was generated outside the body. The contrasting fates of Volta and Galvani are a sanguine lesson in cultivating powerful patrons.

The book progresses through the 19th century with descriptions of the work of du Bois-Reymond, Helmholtz and Bernstein duly covered, but the narrative takes flight on the eve of the 20th century with the triumphs of Cajal and Golgi. Their work, and long-lasting feud, are related in fascinating detail, underlining, as occurs again and again in this marvellous book, how the personality of the researcher drove the direction and intensity of their work. The area that will probably be of most interest to readers of *Physiology News* will be Erlanger and Gasser's pioneering work, leading up to the glories of Hodgkin and Huxley, followed by the explosion in electrophysiology in the latter half of the century.

This is all chronicled in detail, with a host of fascinating (and unknown to me) tidbits relating to the work. If you want to know why the authorship for one of Erlanger and Gasser's classic papers read "Erlanger and Gasser with the collaboration in some of the experiments of George Bishop", and the murky details of why Bishop was not awarded the Nobel Prize to which he was entitled, read on.

The author worked with Andrew Huxley and not only dedicates the book to him, but accurately describes the triumphs of his career. The achievements of Hodgkin and Huxley are often taken for granted nowadays, but the author forensically describes their progress, labours and ultimate triumphs. It is worthwhile noting the confusion and false leads of their contemporaries Lorente de No, Kenneth Cole and John Eccles, to realize just how miraculous their work was. The book concludes with coverage of the patch clamp technique, channelopathies and Rod MacKinnon's work on elucidating the 3D structure of potassium channels.

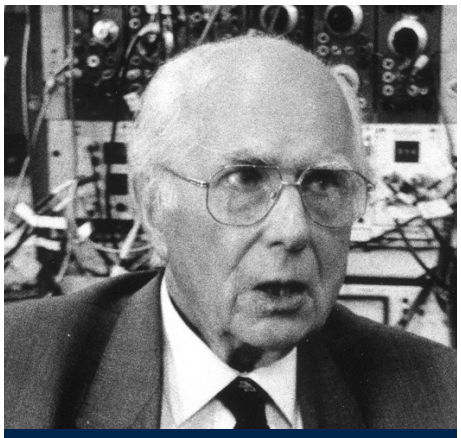
The footnotes to the individual chapters and the references section are worth the cost of the book alone in highlighting long-forgotten or previously unread papers – Rinzel (1990) *Bull Math Biol* **5**, 25-23 being an excellent example of clarity and insight into Hodgkin and Huxleys' work.

This is an excellent book which should be a mandatory purchase for all electrophysiologists and an accessible introduction to the subject for inquisitive students.

Andrew Fielding Huxley

1917–2012

Picture credit: Martin Rosenberg



Andrew Fielding Huxley

Sir Andrew Huxley was an epoch-making pioneer in the physiology and biophysics of nerve conduction, and skeletal muscle activation and tension generation. He was born in London within an illustrious intellectual family, and educated at University College (1925–30) and Westminster Schools (1930–5), and Trinity College, Cambridge (1935–9), his interests leading him to read Part II Physiology in the Natural Sciences Tripos (1938–9). His research began with Alan Hodgkin in 1939 on the properties of the propagated impulse in giant axons of squid. This groundbreaking work on nerve excitability in the Cambridge Physiological Laboratory and the Plymouth Marine Biological Laboratory applied the voltage-clamp technique to characterize the properties of membrane sodium and potassium permeabilities and reconstructed their changes during membrane excitation. This provided the basis for our current understanding of how voltage-gated ion channels generate propagating action potentials. It led to his being awarded the 1963 Nobel Prize for Physiology and Medicine with Alan Hodgkin and Jack Eccles.

This led to a cascade of important discoveries culminating in our current understanding of excitable tissue function. Those bearing upon the fundamentals of channel function included the demonstration of gating currents and their application in characterizing molecular configurational changes underlying channel activation. Demonstration of the unit channel events through single ionic channels underlying the observed conductances led to award of the 1991 Nobel Prize to Erwin Neher and Bert Sakmann, and to recent biochemical characterizations of sodium channel structure and of its gating transitions. Both the voltage-clamp techniques and their associated mathematical formulations were to be generalized to other excitable tissues, including mammalian nerve, and skeletal and cardiac muscle, as well as encoding processes in repetitively firing nerve cells. They also led to mathematical analyses reconstructing the cellular homeostatic effects not only of electrogenic but also electroneutral and osmotic fluxes and metabolic change. Finally, their translational applications bear on demyelinating disease, our understanding of pain and anaesthesia, and of electrophysiological and arrhythmic disease in skeletal and cardiac muscle. These include Huxley's own work on the function of the myelin sheath in vertebrate nerve fibres in saltatory impulse conduction.

Huxley performed groundbreaking work of similar importance on muscle activation and contraction whilst at University College London. He demonstrated the means by which surface membrane excitation in skeletal muscle is transmitted into the fibre interior to initiate myofilament activation by the transverse tubules. This prompted subsequent strategic work clarifying the electrophysiological role of the transverse tubules in spreading excitation into the muscle interior, as well as its molecular coupling processes triggering release of intracellularly stored Ca^{2+}. In the meantime, Huxley turned to the muscle contractile process itself, proposing and establishing the sliding filament theory of muscle contraction through comparing the expected extents of actin and myosin filament overlap with their resulting isometric muscle tension. He then proposed a model for crossbridge interaction for these myofilament interactions, on the basis of their observed tension transients. This proposed crossbridge cycles involving elastic and stepwise-shortening elements driven by actin–myosin binding through a sequence of attachment sites, followed by crossbridge detachment and ATP hydrolysis. This completed his momentous contributions to physiology, as "the mechanical engineering of living things".

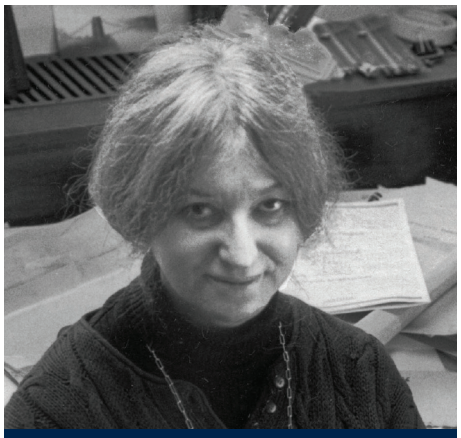
Sir Andrew was elected to the Royal Society in 1955 and was its President between 1980 and 1985. He became Jodrell Professor of Physiology in 1960, then Royal Society Research Professor in University College London in 1969. He was Master of Trinity College, Cambridge between 1984 and 1990, knighted in 1974 and appointed Order of Merit in 1983. He was elected Ordinary and Honorary Member of The Physiological Society in 1942 and 1979 and served on the Editorial Board of *The Journal of Physiology* (1950–57) and its Committee (1957–61; 1970–4). In 1947 Andrew Huxley married Jocelyn Richenda Gammell Pease who predeceased him in 2003. They have five daughters and a son.

Christopher Huang

Anne Warner

1940–2012

Picture credit: Giorgio Gabella



Professor Anne Warner

Anne Warner, who has died aged 71, combined careers as cell physiologist, a science policy maker and, latterly, an initiator and Director of CoMPLEX, a centre for systems biology at University College London (UCL). Born Anne Brooks, she took a degree in physiology at UCL and then worked for her PhD with Otto Hutter at the National Institute for Medical Research, Mill Hill. There she was appointed at the age of 23 to a staff position and carried out some of the classic studies on the pH dependence of the chloride conductance in skeletal muscle.

Her main research was devoted to understanding the role of gap junctions for intercellular communication during vertebrate embryonic development. Her collaborators included some of the major developmental biologists of the '70s and '80s. With her students and colleagues Christine Slack, Susanna Blackshaw, Luca Turin and Sarah Guthrie, her laboratory published a series of papers in *The Journal of Physiology*, *Nature* and *Cell* which mapped out the early electrical events occurring during normal embryo development. She also co-authored with Peter Baker, Roger Tsien and Tim Rink papers on many of the earliest projects which made the critical link between calcium and cell organisation.

Following appointments at the Middlesex Hospital, in Lewis Wolpert's biology department, and then at the Royal Free Hospital School of Medicine when it was still in Hunter Street in Bloomsbury, Anne took up an appointment at UCL in 1976 in Geoff Burnstock's Department of Anatomy and Developmental Biology where, in 1986, she became Professor of Developmental Biology. That same year she was awarded the Royal Society Foulerton Professorship.

Although she maintained her interest in development, there can be little doubt that much of her subsequent energy went into committee work and scientific policy. Sitting on councils including NERC, the Lister Institute and the Roslin Institute, she was clearly much in demand; many can remember the speed with which she could deal with any application. As a Vice President of the Council of the Marine Biology Association at Plymouth she undoubtedly steered the MBA through particularly difficult financial times in the 1990s. She had a major influence in the creation of the Cell Physiology workshop in 1984 (originally known as the Microelectrode Techniques workshop), a course that has created many cohorts of cell physiologists in the UK and abroad.

Anne had a penchant for academic gossip, whisky and cigarettes, probably in that order. She very much saw herself as part of a UCL family and was extremely loyal to it and to her friends. She had the uncanny ability to home in on conversations, preferably in proximity to a bottle of wine. She could usually be spotted in the UCL quad pacing up and down deep in thought with a cigarette held jauntily in one hand. She was formidable in her determination and, once her gaze fixed on you through her carriage-lamp spectacles, it was quite hard to refuse to do what she asked. Mobility became difficult for her during her last years, but this did not stop her firing off emails of advice and requests for information, often on an hourly basis. Her husband, Michael, a marine engineer whom she met as a student, when both were in the UCL Dramatic Society, predeceased her by just a few months.

Jonathan Ashmore

Hilda Tracy

1927–2010

Hilda Tracy

Hilda Tracy was a longstanding Member of The Physiological Society, who performed seminal work on the isolation and characterization of the acid-secretory hormone gastrin, the first gastrointestinal hormone to be sequenced. She was born on 14 October 1927, and grew up in Birkenhead, one of a family of four children. After leaving school she worked at the University of Liverpool, ultimately in the research laboratory of Rod Gregory. Encouraged to enrol as a university undergraduate, Hilda took a degree in medicine which she accomplished with distinction, winning several medals and prizes.

In 1958 Hilda joined the academic staff of the physiology department in Liverpool and continued to work in partnership with Rod Gregory until his death in 1990. In the late 1950s they had attempted to repeat the work of Simon Komorov, who was the first to report a histamine-free, gastrin-rich stomach extract. However, the method proved unreliable so Gregory and Tracy devised a whole new extraction and purification procedure that utilized weekly, hundreds of pig stomachs collected from a local abattoir. These heroic efforts culminated in the resolution of two pure peptides in 1962 that were subsequently sequenced as two heptadecapeptides differing in the presence or absence of a sulphate group on the solitary tyrosine residue. They continued to isolate gastrin for many years and provide it to countless collaborators worldwide who were keen to study the biology of this new peptide. Their scientific partnership was very much an equal one, a fact not always appreciated at the time – perhaps due in part to the then prevailing perception of the place of women in science. Hilda played a lead role in the structure-activity studies on gastrin which revealed the unexpected finding that the carboxyl-terminal tetrapeptide amide possessed the full biological properties of the intact peptide. It was also she who hit upon the idea that gastrin might be the active factor in clinical cases of patients with intractable peptic ulcer and an endocrine tumour of the pancreas, first described by Zollinger and Ellison in 1955. Gregory and Tracy were subsequently able to isolate the active factor from pancreatic Zollinger-Ellison tumours, showing it to be identical to gastrin from the stomach and thus laying the foundation for gastrin radioimmunoassay to become a reliable diagnostic test for Zollinger-Ellison tumours. Hilda was rigorous in the pursuit of scientific excellence, and forthright in discussion, but she did not devote much energy to self-promotion, which is perhaps why outside the main players in her field, she remained rather less well known than was justified.

Hilda was a popular lecturer and tutor; students recognized in her someone with a thorough understanding of the subject and the all too rare ability to make it both accessible and interesting. She was a valued member of the physiology department, independently minded with a practical and common sense approach to problem solving. Hilda was always happy to impart advice and help to junior colleagues and was a ready and fierce supporter of the underdog. She was unwavering in her sensitivity to injustices to students or junior researchers and reliably robust and even outspoken in their defence.

During the early part of her career, Hilda married and brought up two children, and she remained devoted to her family. After her retirement in 1993 she was able to spend more time on her lifelong passion for her garden and the countryside; she also developed a keen interest in painting. Hilda remained fit and active long into her retirement, walking her dog for two hours every day right up until her final illness which she bore with characteristic dignity.

Rod Dimaline

The Society also regrets to announce the deaths of:

Sir Gabriel Horn

was Emeritus Professor of Natural Sciences (Zoology) at Cambridge University. He was 84 and was elected a Member of The Society in 1963.

Stephen O'Neill

worked in the Manchester Cardiovascular Group at the University of Manchester, and was elected a Member in 1990.

Yves Laporte

one of the most eminent physiologists of the 20th century, who was elected an Honorary Member of the Society in 1984.

Full obituaries can be found on The Society website at:

www.physoc.org/late-members

Journal updates

The Journal of Physiology

New editors

The Journal of Physiology has added the following individuals to its team of editors:

Senior Editors

Gianmaria Maccaferri, Chicago, IL, USA

Ingrid Sarelius, Rochester, NY, USA

Editors

Jaideep Baines, Calgary, Canada
Kenneth Baldwin, Irvine, CA, USA
Derek Bowie, Montréal, Canada
Peying Fong, Manhattan, Kansas, USA
Constancio González, Valladolid, Spain
Virginia Huxley, Columbia, MO, USA
Kathleen Morgan, Boston, MA, USA
Ruth Murrell-Lagnado, Cambridge, UK
Louise Robson, Sheffield, UK
Hartwig Siebner, Copenhagen, Denmark
Sam Wu, Houston, TX, USA
Gary Mawe, Burlington, VT, USA

Experimental Physiology

Editor's Choice 2012

Recent advances in genome sequencing, bioinformatics analysis, *in vivo* genetic manipulation including optogenetics, and advanced imaging technologies have provided powerful new tools with which physiologists can explore fundamental questions and opens a whole new era in physiological and pathophysiological research.

The papers in this virtual issue have been selected as examples of the integrative and translational research recently published in *Experimental Physiology*. These papers reflect the enhanced scope of the journal which takes on the challenge of publishing research that addresses major questions in physiology by using novel approaches and techniques.

http://bit.ly/EPeditorschoice

New Deputy Editor-in-Chief USA

Mark Chapleau (Departments of Medicine and Molecular Physiology, University of Iowa, and the Veterans Affairs Medical Center) has been appointed as Deputy Editor-in-Chief USA for *Experimental Physiology*. He will be working to improve the profile of the journal in the USA. He has served as a reviewing editor for the journal since 2009.

Robert Unwin of University College London has also joined *Experimental Physiology* as a new member of our team of editors with expertise in the area of renal physiology.

	Journal of Physiology	Rank (of 79)	*Experimental Physiology*	Rank (of 79)
Impact Factor	4.881	8	3.211	24
5-Year Impact Factor	4.988	5	3.18	24
Immediacy Index	1.386	4	0.885	8
[2011] Articles	420	3	122	30
Cited Half-Life	>10.0	1	5.8	27
Eigenfactor Score	0.08283	2	0.01076	26
Article Influence Score	1.888	7	1.045	25

Stand up for science

Do you know someone who has promoted sound science and evidence? Nominate them for the John Maddox Prize for standing up for science.

The John Maddox Prize will reward an individual who has promoted sound science and evidence on a matter of public interest. Its emphasis is on those who have faced difficulty or hostility in doing so.

The prize is £2000. An announcement of the winner will be published in *Nature*.

The deadline for nominations is midnight on 20 August 2012.

Full details and a nomination form are available online at **www.senseaboutscience.org/pages/john-maddox-prize.html**

Society Members speak on the Olympics

The London 2012 Olympic Games meant that everyone wanted to hear what Society Members had to say on the physiology of elite athletes.

Alun Williams of the Manchester Metropolitan University spoke to Agence France-Presse about gene doping at the Olympics.

Bengt Saltin of the University of Copenhagen explained fast-twitch and slow-twitch muscle fibres to news agency Reuters ahead of the 100 metres sprint final, while Steve Harridge of King's College London helped out the *Independent* on the same issue.

> "WADA should focus on drugs that are clearly performance enhancing in the sports where they are clearly performance enhancing"

When a US judo player was expelled for using marijuana, Michael Joyner, researcher at the Mayo Clinic in Minnesota in the United States, through Reuters, told the World Anti-Doping Agency to "focus on drugs that are clearly performance enhancing in the sports where they are clearly performance enhancing."

Ron Maughn of Loughborough University spoke to the *Guardian* about the collision of an Islamic festival and the Olympics: "Everyone tends to assume that performance is going to be affected by Ramadan, but there's nothing unusual about playing sports in Ramadan."

No doubt many more of you leant your considerable expertise to the media during the games. We'd love to hear when you get physiology into the news, so please let us know, via Twitter, Facebook, or by email (**news@physoc.org**), so we can spread the word.

Biology week: Physiology Friday

The inaugural Biology Week will run from 13 to 19 October 2012, and as part of this, we have co-opted 19 October as Physiology Friday. We would encourage as many of you as possible to run an event on that day. Whether it's an outreach event, a special seminar, or even a physiology-themed bake sale, please help us make Physiology Friday go with a bang!

We also have two competitions:

- 'Vodcast' competition; video yourself, your lab or whatever else you want, to tell us what physiology means to you in less than two minutes. The deadline for entries is 30 September.
- 'The holy grail of human biology research', writing competition for under 19 year olds. It will be a chance for teenagers to tell us, in 200 words, what advances they'd most like to see in physiology and the human sciences. Deadline for entries: 14 October.

Winners will be announced on Physiology Friday. See **www.physoc.org/biology-week** for more.

Would you like to host the next YLS?

The Young Life Scientists' Symposium (YLS) is a scientific symposium organised by early-career scientists for their peers. The meetings provide emerging scientists with an opportunity to network and build new contacts.

Teams of early-career scientists can apply now to organise YLS 2013 on a scientific theme of their choice. All that is required is that the theme is relevant to each of the three sponsoring societies: The Physiological Society, the Biochemical Society and the British Pharmacological Society.

If you would like to bring YLS 2013 to your institution, please visit www.physoc.org/postgraduate-early-career

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