PN
Physiology News

Issue 90 / Spring 2013

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Cover image: *Conducting a maximal oxygen consumption test on a trained cyclist for a prolonged exercise study.*

Credit: *Jill Barnes, Mayo Clinic, USA*

Physiology News

We welcome feedback on our membership magazine, or letters and suggestions for articles for publication, including book reviews, 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

Mike Collis

Welcome to the first edition of *Physiology News* for 2013. This year is shaping up to be a busy and historic one for The Society, with relocation to Hodgkin Huxley House (see page 6), the launch of the new journal, *Physiological Reports* (interview with the editors on page 37), and the IUPS congress in Birmingham (preview on page 14).

A number of articles in this edition of PN relate to exercise, with differing views on the important question, is exercise good for you and inactivity a 'disease'? There is, of course, convincing evidence from major population studies for lower all-cause mortality in those with higher activity levels or cardio-respiratory fitness. But what are the reasons for this and which is the chicken and which the egg? Whilst exercise can have beneficial effects on blood pressure and on biomarkers for atherosclerosis and diabetes, these only account for about 60% of the reduction in risk. Conversely, exercise can have adverse effects on these traditional biomarkers in some individuals. So what else is going on and are we measuring the right things? Exercise has numerous additional effects that could be beneficial for the cardiovascular system some of which are known, e.g. increased vagal tone, pre-conditioning and improved endothelial function. So perhaps we need a new set of biomarkers to assess these. What is important for me and you is whether population-based studies can be applied to all, or do genetic variations mean that 'therapeutic' exercise regimes need to be tailored for each individual. New multidisciplinary collaborative projects are being set up to answer some of these important questions. In the meantime I will continue to exercise. Whether walking, cycling, swimming, etc, extend my life or not, they do make me feel fitter, livelier and happier. Quality of life is surely at least as important as length.

Last year *Physiology News* was redesigned. The editorial board of *Physiology News* have been very active considering how the magazine has developed and our objectives for its future. The main purpose of *Physiology News* is to be enjoyable, useful and informative for our Members. We also hope that it reaches those who have an interest in physiology but who are not Members (perhaps it will encourage them to join!). Finally, we hope that the magazine will make complex topics in and around physiology accessible to students, researchers and teachers of biological sciences. We think that the redesign of *Physiology News* has helped us towards these goals, but we can make further headway in some areas and are, with every meeting of the editorial board, honing our approach. Whilst we believe that content is much more important than presentation, a constant source of debate amongst the editorial board is our use of imagery. Ideally, we would like to have images that show physiologists at work or images of physiological science. It is difficult to access high quality images of this type and this is an area where Members may be able to help us by submitting appropriate material (see page 7 for our pilot photography competition).

We recently ran our first themed issue (education, PN89). Our summer issue this year will have an international theme (to coincide with the IUPS meeting) and autumn will have an industry theme, exploring what it is like to work in industry, how to collaborate with industry and whether it is possible to move from the academic sector into industry and vice-versa. We are keen to have content direct from Members – article proposals, but also responses to articles in PN, or to developments in physiology. PN should be a forum for discussion around practice and policy in physiology. So email us if you might like to contribute.

Finally, 'Feedback is the breakfast of champions', as they say, and we have had some very useful comments on the magazine from a few Members of The Society. But we want more. We welcome your feedback at any time, but right now The Society is running a membership survey (page 7) and I look forward very much to seeing your opinions of *Physiology News*.

The Society brings Katz, Starling, Hill and Sherrington to Hodgkin Huxley House

Having relocated in December 2012, The Society is now based at Hodgkin Huxley House (HHH). The Society completed the purchase of 30 Farringdon Lane, London, in summer 2012 and had the premises refitted to be a 'home for physiology' in the UK.

As well as a high-spec auditorium for lectures, seminars and social events for up to 75 guests, HHH also has flexible space for board meetings, consisting of three rooms with movable walls.

Society Members voted online to name the auditorium after Bernard Katz, and the three meeting rooms after Ernest Starling, AV Hill and Sir Charles Sherrington. These four figures were nominated for their close ties to The Society as well as their immense contributions to physiology. The Council endorsed the results of the vote and are looking for other ways to profile and reflect on other physiologists in the building going forwards.

Several other organisations concerned with life sciences have already hired these meeting room spaces to successfully host their own events, and two tenant organisations now occupy the upper floors of HHH (see The last word, p52).

Watch out for a programme of Society events at HHH to be announced later this year.

2013 Honorary Members: Call for proposals

We are now seeking nominations for Honorary Membership of The Society. Honorary Membership may be awarded to any eminent physiologist, and the privilege is not just limited to current Members of The Society.

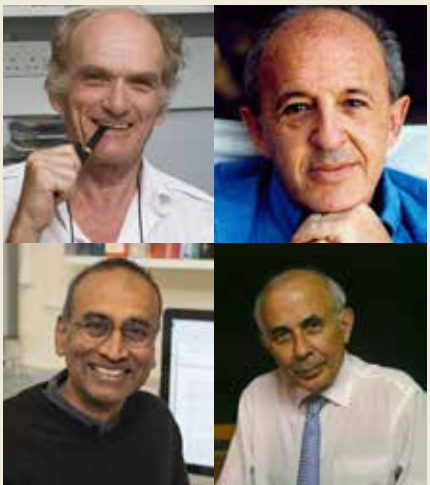
If you know of any physiologists who can be considered '*persons of distinction in science who have contributed to the advancement of physiology or to the work of The Society*', please send us their name and your statement of support. Your proposals will be considered by the Nominations Committee who will advise Council on formal nomination.

The new Honorary Members will be announced at the 2013 Annual General Meeting.

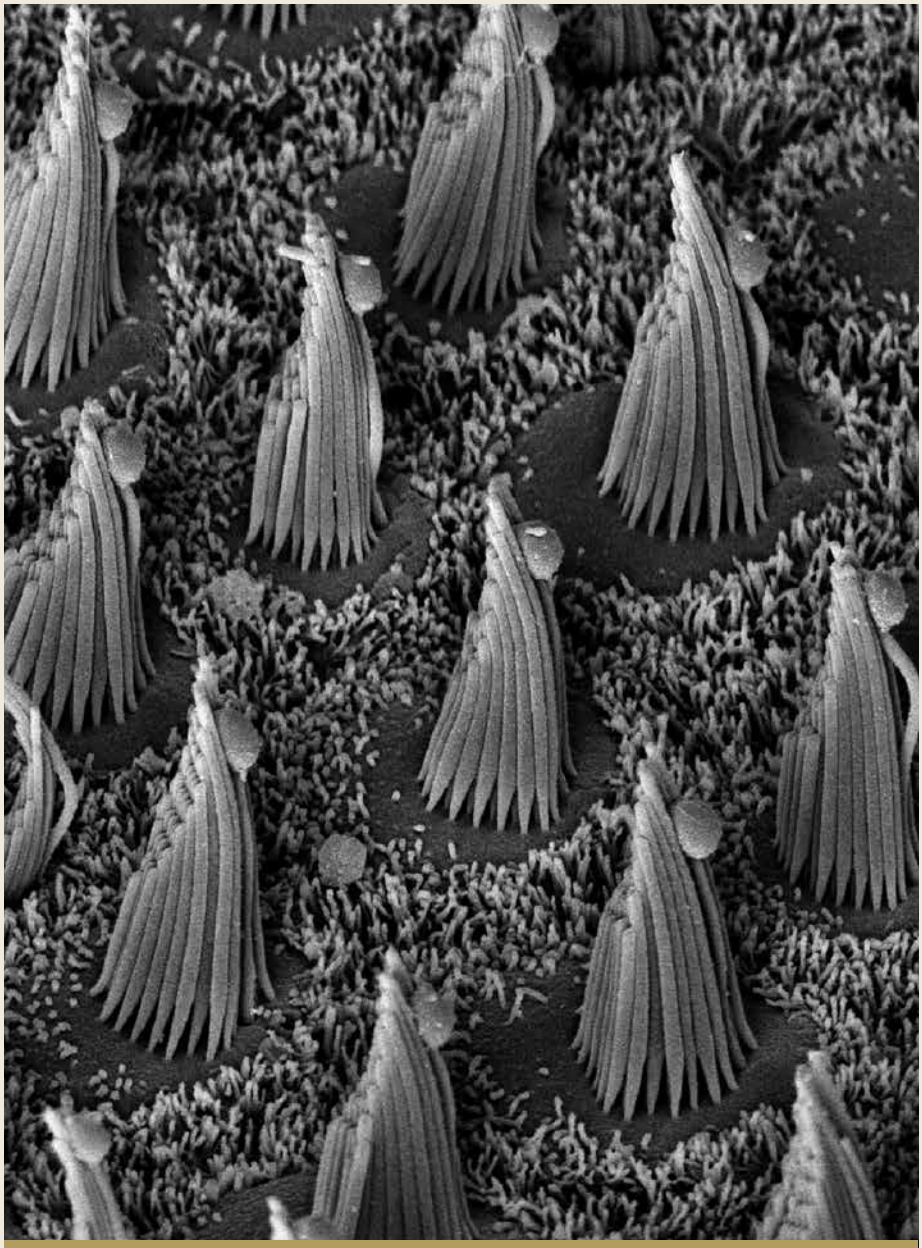
Honorary Members have the same rights and benefits as Ordinary Members of The Society, but are not called upon to pay annual subscriptions. In addition, Honorary Members are also eligible to receive a print subscription to *The Journal of Physiology* free of charge as well as free attendance at Society meetings.

Please submit your proposals at www.physoc.org/honorary-membership

The deadline is **19 April 2013**.



Some of the 2012 Honorary Member electives, clockwise from top left: David Colquhoun, John Nicholls, Semir Zeki and Venki Ramakrishnan.



The mechanoreceptive hair bundles protruding from hair cells of the frog's inner ear transduce accelerational and acoustic stimuli into electrical signals that are forwarded to the brain.

Preparation made and picture taken by Andrei Kozlov, Thomas Risler, Armin Hinterwirth, and Jim Hudspeth.

Physiology photo competition

Do you have an image of historic histology? Have you captured a concentrating colleague on camera? Is your micrograph magnificent?

We are excited to launch our Members' image competition, with a £100 Amazon voucher prize for the overall winner, and £50 vouchers for two runners up, along with publication in *Physiology News* for all commended entries.

Images will be shortlisted by a panel including Society President, Jonathan Ashmore, and will then be taken to an online vote by Members.

All images submitted may be used in *Physiology News*, the Society website, www.physoc.org, or other Society promotional materials, and will be entered into our image archive for future use (every use will be credited).

Your images may also be reproduced as artwork to adorn the walls of The Society's new headquarters, Hodgkin Huxley House. If so, you would be offered a canvas print as a 'thank you'.

Entries must be labelled with the entrant's name and image files must be at least 72 dpi and between 1MB and 5MB. Where an image focuses on an identifiable individual, or a group in a non-public setting, signed model release forms are required. You can download this simple form from our website, and see our terms and conditions, at www.physoc.org/photocompetition.

Send your image to photos@physoc.org by 14 June.

Have your say on your Society

We are calling on all Members to share their opinions on The Society through our 2013 Members survey. The survey is online now at www.surveymonkey.com/s/memsurvey2013.

It will take less than 15 minutes to complete the survey and you will be entered into a prize draw to win one of two 16 GB iPad Minis.

We hope very much that you will let us know your thoughts on our journals and membership magazine, our website, our events, and our work to promote the interests of physiologists and the study of physiology.

Congratulations to the winners of the 2012 Undergraduate Prize for Physiology

Each year, The Society recognises the academic achievement of undergraduates in physiology by awarding prizes to students with the best final year project or overall performance at their university. In doing so, we aim to encourage their continued engagement in physiology and develop their contacts with other researchers in the field.

In 2012, 42 students across the UK and abroad were awarded with the Undergraduate Prize for Physiology, which bestows £100, a certificate of achievement and eligibility to apply for one year's free membership at The Society – providing access to all the benefits that membership offers.

Undergraduate Prize winner, Matthew Jones, a final-year medical student at the University of Southampton, said, "Winning the undergraduate prize for my research in critical care/anaesthesia during my fourth year of medical school, came as a complete surprise. I had no idea I was even being considered and am grateful to my clinical supervisor for recommending my work for consideration. It was an honour to be able to come away from my research year with such an accolade and it has helped confirm my interest in physiology, something I hope to carry on post-graduation, into my career as a doctor."

Kseniia Afitska of Taras Shevchenko National University of Kiev, Ukraine, said, "It was a great surprise to win. I am very happy and proud. And, importantly to me, my research supervisor can be proud of me. Winning the prize opens new possibilities in my studies. I'm over the moon."

A full list of the winners can be found on The Society's website (www.physoc.org/prizes), along with more information about the prize scheme. A call for nominations for the 2013 prize will open later this year.

We would like to congratulate all the winners on their outstanding work during their degree and wish them every success in the future.

Voice of Young Science media training

Affiliate Member Lissa Herron, University of Edinburgh, reports on the VoYS media workshop

Supported by Sense about Science, VoYS provides media training tailored for young researchers to help them to work with journalists and to get their voices heard. I attended a workshop in Glasgow last year and found that, unlike other workshops that train you to work with the media, the VoYS workshop provided a chance to discuss the role of the media in reporting science and how to react to bad science in the media.

We heard from academic researchers who recounted their experiences of working with the media and from journalists who highlighted their motivations for writing science-based stories and the restrictions within which they have to work.

These speakers were complemented by talks from a press officer and Sense about Science representatives, who gave us practical advice for getting our voices heard. The workshop also allowed ample opportunity for question and answer sessions with the panellists, and for more general discussion about a young researcher's role in science communication.

I thoroughly enjoyed participating in this workshop and recommend attendance for any young researchers interested in communicating their science to the wider world.

Participants at the Glasgow workshop, 16 November 2012.

The Physiological Society is a partner of VoYS, supporting not only the media workshops, but also the campaigns, myth-busting activities and network of early-career researchers.

VoYS is running five workshops in 2013. Society Members receive priority booking for these workshops. For more information, visit The Society's website: www.physoc.org/voice-young-science.

Policy Corner

Policy makes a difference

Mary Morrell

Chair, Policy Committee

The European Directive 2010/63 on the 'Protection of Animals in Scientific Experimentation' came into force on 1 January 2013. This is of direct relevance to Members of The Society, and as such the Policy Team would like to thank all our Members who responded to our call to write to your MP at the end of 2012.

I am pleased to let you know that we had an amazing response with over 70 MPs being contacted, some more than once! It was interesting to see which MPs responded. The legislation was debated in the House of Commons on 3 December 2012 and was passed without a hitch. This was better than we hoped for and The Physiological Society's contribution was openly acknowledged by Dr Julian Huppert (Cambridge; Liberal Democrat), which goes to show we can make a difference - one letter at a time.

If you would like to engage with your MP further as part of our MP engagement scheme, please visit our website (www.physoc.org/mp-engagement-scheme). We believe it is crucial to engage with policy-makers to help inform them about the realities of animal research.

Watch this space for the next Policy Committee project!

Education policy update

The voice of physiology in education reforms

Following the UK Government's proposals to reform the National Curriculum in England alongside GCSEs and A-levels, The Society's Education and Outreach Committee has been working to ensure that physiology is represented accurately, and that the new qualifications accurately assess the skills important for progression in physiology beyond school.

In this, The Society is collaborating with SCORE (Science Community Representing Education) and the Science Council. The following is a brief outline of The Society's recent engagement in these policy areas.

A-level reform

In June 2012, Ofqual (the regulator of qualifications, exams in England) launched a consultation on proposals for the reform of A-levels, which included changes to qualification structure, resit rules and the role of higher education institutions in the development of new A-levels. The Society fed into joint responses to this consultation by SCORE and the Science Council.

Ofqual published its findings in November 2012, announcing the removal of January exams for AS and A-levels from September 2013. Further key areas of change were announced by the Secretary of State for Education in a letter to Ofqual in January 2013. These included a move to a linear A-level with all assessment at the end of two years, retaining the AS level but as a standalone qualification, and pla ns to establish an advisory body – created by the Russell Group – to provide advice to Ofqual on the content and assessment of A-levels.

The Society is keen to ensure that this advisory body reflects the diversity of institutions across the HE sector and will continue to input into these reforms, which are due to be implemented for first teaching in September 2015.

National Curriculum review

The Society plans to continue inputting into the National Curriculum review, primarily through SCORE, wherever possible. At the time of writing, the draft Key Stage 3 (age 11-14) programme of study for science had just been released by the Department for Education (DfE) for consultation, and announcements were expected regarding the draft Key Stage 4 (age 14-16) science programme of study.

Key Stage 4 (GCSE) reform

In September 2012, the DfE released a consultation, which outlined proposals to replace the current GCSEs with English Baccalaureate Certificates (EBCs) and introduce a franchise system whereby only one awarding organisation (AO) would be awarded with a contract to offer qualifications in a particular EBC subject for five years. The Society contributed to a joint response to this consultation with SCORE.

After the consultation closed, the Secretary of State for Education announced that these plans would be abandoned in favour of reforming the existing GCSEs as set out in the consultation document: these include a move to linear qualifications with exams taken at the end of two years and more problem-solving questions in science assessments.

Further to this, The Society has been inputting into a set of guidelines that SCORE is producing for AOs, Ofqual and the DfE, which express clearly what the characteristics of a science Key Stage 4 qualification should be. The aim of the guidelines will be to inform the development of these qualifications transparently and fairly across all parties. They will be made publicly available in February 2013.

The Society will continue feeding into the development of the new Key Stage 4 science qualifications as and when further announcements are made.

If you'd like to get involved with any of this education policy work, we'd be delighted to hear from you at education@physoc.org.

Student access to lecture material: How to avoid copyright pitfalls

Michael Evans
Keele University

These days lecturers are caught between a brick wall and a hard place in respect of copyright law and responsibility to the students they are teaching. Students quite naturally like to be able to peruse a lecture both before and after it has been given, and for this they ask for the lecture to be uploaded onto the University intranet (Virtual Learning Environment, VLE) as a PowerPoint presentation or a PDF. But such an act, if it concerns a lecture that includes scanned or downloaded diagrams from textbooks or other published sources, will almost certainly infringe copyright law designed to protect the creators of the work (Copyright, Designs and Patents Act 1988, www.legislation.gov.uk/ukpga/1988/48/contents). To make matters worse, a lecturer has nowhere to hide as it is s/he who is infringing the law, not their employer the University.

This problem led me to investigate the possible ways forward, and none of them are particularly encouraging. In theory, one can get permission from publishers to publish their images, but this takes time (often a long time) and will probably incur a charge, and both will add up if this approach were to be followed over a complete lecture set. In my case at present, this amounts to about 30 lectures, and roughly each one contains 10–15 images. My university, and I expect most UK universities, has a digitization service that is licensed to copy material, with some restrictions, from the library's collection. This works well, but again the time involved to precisely identify exactly what is to be copied and fill in the online form all adds up. Having done my PhD "in the old days" when diagrams were often drawn by hand, I have on occasions simply taken a sheet of paper and drawn the essential features of the image(s), scanned them, and produced a special online version of my lecture which can be uploaded onto the VLE legally (providing the original sources are acknowledged). But while doing this one is bound to ask "what am I doing?" with the usual persistent concern about the time taken, and that's before the students feedback on their quality.

But perhaps there is light at the end of the tunnel? The central complaint outlined above concerns the large amount of time necessary to comply with copyright law in order to grant students the ability to download lectures that include images taken from published sources. But is this a useful use of their time? Again, harking back to the old days, we used to say that we were at university to *read* Physiology, or whatever "science allied to Physiology" we were taking (to use the The Society vernacular). Might they be better off seeking out the original sources used in their lectures in the library, or online, and using that as a way to learn? Just because a VLE provides the ability to upload lectures including diagrams and images for student consumption doesn't mean that this is its primary use, particularly in view of copyright law and what that means to lecturers.

I'm drawn to a single conclusion, and that it is best not to try to upload images onto the VLE. Perhaps a simple word document will suffice, just detailing the main points including the best sources. It could be a win–win situation in the long run, with lecturers both saving valuable time and not being drawn onto the wrong side of the law, students learning better (and perhaps attending more lectures), and the creators of the work being content that their legal rights are not being infringed.

In vivo short courses: Giving students first-hand experience and knowledge

Mike Collis

Richard Apps

University of Bristol

Physiologists and pharmacologists need to understand the appropriate use of animals in research and those who can perform *in vivo* experiments are essential in many areas of biological research. *In vivo* skills are needed in government and academic research labs that investigate basic physiology, ageing, diseases and their treatments. Such skills are essential for the translation of genomic information into functional significance, particularly for researchers using transgenic animals. They are also needed for drug discovery and development in both the pharmaceutical and biotechnology industries. However, the opportunity for students of the biological sciences to learn about and experience *in vivo* experiments in the UK is severely limited, primarily by the high cost (in both money and time). In response to this, The British Pharmacological Society (BPS) and The Physiological Society introduced short, one week, *in vivo* courses in 2001. These courses were to provide an intensive *in vivo* research training experience for undergraduates and postgraduates from the UK and ROI, particularly when their home institution could not provide this. Since their introduction, the courses have proved extremely popular with both undergraduate and postgraduate students and are consistently oversubscribed. As of 2011, students from 42 different universities have attended them.

In vivo courses are expensive to run and they require a high staff to student ratio. The short courses cost about £2000 per student, which also includes the costs of student travel and accommodation. This is much more than universities can afford and consequently the courses have been funded by the two societies, industry, the Biotechnology and Biosciences Research Council (BBSRC) and the Wellcome Trust. In 2013, the Medical Research Council (MRC) joined the funding group, reinforcing the increasing recognition of the importance of providing these courses and of offering students an understanding of *in vivo* research.

Each course has two components: a Home Office training course during the Easter vacation and an experimental course during the summer vacation. Students attending the courses can therefore apply for a Home Office personal licence to allow them to participate in animal experiments. However, the courses are not primarily about gaining manual skills. They are designed to teach the students to understand when it is essential to use an animal in an experiment and when it is not. The ethics of animal experimentation are discussed and there is a strong emphasis on the application of the 3 Rs (Replacement, Reduction and Refinement of animal experiments). All *in vivo* experiments should be appropriately designed so that the data obtained is statistically valid and these aspects are also an important part of the courses. Finally the students have hands-on experience of participating in *in vivo* experiments and the subsequent analysis of the data obtained, providing them with a valuable insight into the practical issues and biological variability inherent in whole animal research.

Three courses were originally offered: at Kings College London, University of Bristol and University of Glasgow. In 2013 this number increased with additional new courses at University of Glasgow and Strathclyde University. The five short courses which are now offered have many features in common and illustrate how *in vivo* experiments are important in cardiovascular biology (Glasgow, Bristol, Kings), inflammation (Strathclyde), nociception (Kings) and neuroscience research (Bristol, Glasgow).

Applications to attend the courses are invited each autumn via The Physiological Society and BPS websites and are considered on a competitive basis. Applicants do not need to be a Member of either society to apply for the courses, although we hope that attendees will join if they are not already a Member.

The value of the courses is best illustrated by the feedback from the attendees, the majority (~70%) of whom have gone on to use their *in vivo* skills in further research.

"The course was highly influential in my career path. It provided me with highly sought after skills and an insight into a side of medical science few undergraduates get to see. Without the course, it may have been the case that I wouldn't have been offered two PhD in vivo *studentships."*

"This course has been one of the most influential aspects that has made me driven to pursue a career in science. I loved the whole experience, and the first class teaching from our supervisor will ensure in vivo *work remains a high priority in the minds of all those who attended the course."*

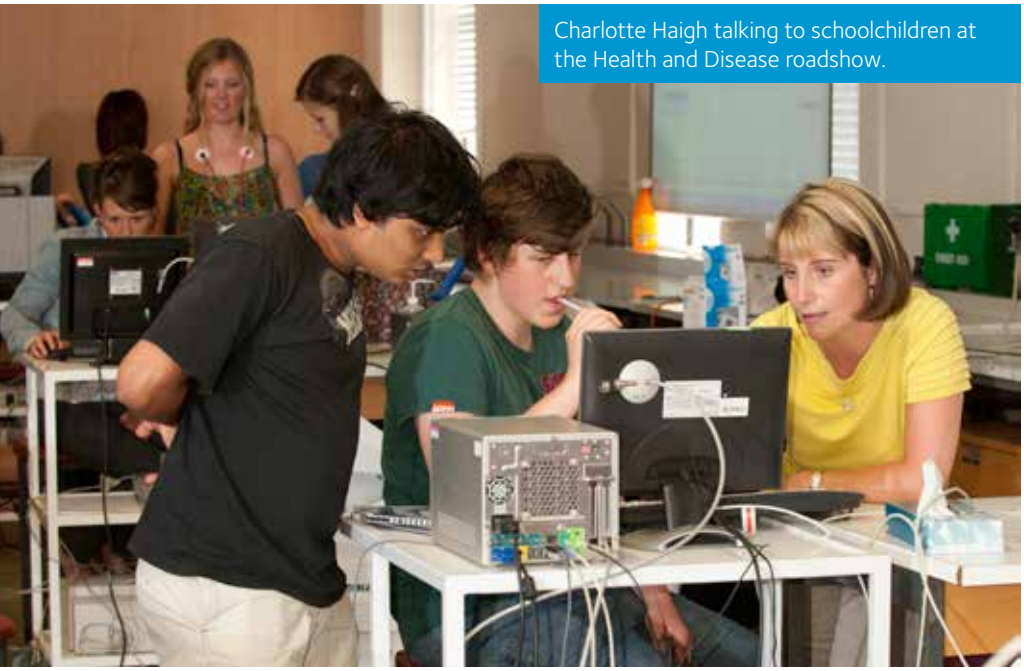
"The course broadened my understanding of in vivo *research. It also allowed me to complete an* in vivo *dissertation project which gave me some excellent* in vivo *research experience. Following the course and my dissertation experience, I have become increasingly aware of the power of* in vivo *research in furthering our scientific understanding; and would definitely consider future work within this avenue should it be applicable to my line of research."*

"In an ideal world, all students would have the chance to take part in a course like this. It is exactly what is needed for students to decide to stay in research."

"I gained a much better understanding of what is involved in in vivo *work and the arguments for and against."*

A group of students on the *in vivo* course at University of Bristol in 2004.

The impact of engaging



Charlotte Haigh talking to schoolchildren at the Health and Disease roadshow.

Lewis Dean

Outreach Officer,
The Physiological Society

Increasingly, researchers are being asked to describe the economic and societal impacts of their work, alongside the academic goals. With the impact of 'impact' on funding decisions and career progression looking set to grow still further, one important, measurable societal impact is public engagement.

There are plenty of phrases that are used to describe what I am talking about – 'science communication', 'public engagement', 'science outreach', 'informal science learning' – and each does have its own nuanced definition, referring to different approaches or methods. What these phrases have in common (and what this article is about) is the broadest idea: getting out there and interacting with people.

However, engaging with public audiences is about more than just funding proposals. Stuart Allan, University of Manchester, has been involved in a wide variety of public engagement projects. He explains, "If we want to gain public support for the most recent advances and importance of science to society then we must have scientists willing to go out and talk about it". Engagement is a two-way process; Charlotte Haigh, University of Leeds, approaches it as, "Inspiring anyone who is interested in what physiology research is about and very much listening to their stories."

"We must be willing to take on board the views of the public," says Stuart. Whilst many of us are happy to agree that science is important to society, we must also acknowledge that society affects how we do our science (Stillgoe, 2009).

There are plenty of opportunities available to get involved with engagement. Some may appeal to you, others may not; Lauren Hughes, University of Bristol, advises, "Just be yourself and get involved in the public engagement activities that you are passionate about".

Engagement is meant to be a rewarding, enriching and educating experience for all parties involved, including the academics. Recently The Society sponsored four Bright Club evenings – stand-up comedy performed by academics. Devised at UCL and now run in towns across the country, the aim is to bring researchers together with 20-40 year olds, who have no existing contacts with academia, in a venue outside a university. But it's clearly not for everyone; whilst some may jump at the chance to do several minutes of jokes about their research, for others it probably sounds like torture.

Alongside her teaching role at Bristol, Lauren Hughes has helped develop and deliver hands-on physiology experiments in the Mobile Teaching Unit (MTU), a heavy goods vehicle that converts into a science classroom. With colleagues and students she travels to schools and colleges nationally and attends a number of science festivals. The MTU is a large capital investment, but there are many smaller projects also engaging with public audiences. In October Charlotte Haigh and colleagues ran a stand in a local shopping centre, taking the blood pressure of members of the public, explaining the results with models and posters, and answering questions. The 'Brain Bus' project devised by Stuart Allan and colleagues has run in schools, libraries and train stations across Manchester; as Stuart puts it, "Take the science to the public, rather than the public coming to the science".

So how do you start? Charlotte Haigh is clear: "Don't be afraid, just do it!" Whilst it can seem daunting, remember there are plenty of activities already out there that you can get involved with. If you want to devise your own activity, speak to people who have some experience running events. Remember that The Society offers grants and we can advise on project design. If you want to hear about the events that we are carrying out and other relevant opportunities, you will soon be able to update your profile online to include your engagement interests or you can email me. I urge you to have a go, because, as Charlotte Haigh puts it, "When you see that first face light up because they are interested in what you have said, there will be no turning back, you'll be thinking of what else you could inspire them with!"

References

'Pathways to Impact' RCUK website http://www.rcuk.ac.uk/kei/impacts/Pages/meanbyimpact.aspx. Accessed 24 Jan 2013

Stilgoe, J. (2009). *Citizen Scientists. Reconnecting Science with Civil Society.* Demos

Stuart Allan talking to children at the 'Body Experience' event run across the University of Manchester.

The Society's story: Keeping our history alive

The HAC stand at the Edinburgh Meeting 2012 starred a Carl Ludwig Kymograph (as polished and prepared by Jane Haley).

David Miller

Chair, History & Archives Committee (HAC)

From the earliest days, The Society has sustained an interest in its own history. This includes how and why The Society was founded, the background to our owning *The Journal of Physiology* and *Experimental Physiology*, how we ran and run our scientific meetings, the forging of our international membership and our collaborations. These aspects often entwine with the careers and collaborations of prominent personalities amongst the membership. Furthermore, as with any organisation, there are more formal elements to the archiving of paperwork and records. An abiding interest is to clarify how the intellectual discipline of physiology can be understood better through knowledge of these historical strands.

In 1989, the movement of The Society's archives from Churchill College in Cambridge to the Wellcome Institute in London prompted The Society to formally task a subcommittee with ensuring that the history and archives of The Society, in all senses, were secured, maintained and promoted to the membership and wider. Tilli Tansey (Queen Mary, University of London) has been The Society's Honorary Archivist ever since. The function of HAC was substantially reinvigorated in 2006 by Dafydd Walters, my predecessor as Chairman.

One sombre element of HAC's remit is to ensure that obituaries are produced to record the life and work of recently deceased Members. However we also conduct The Oral History project, which is a series of interviews where distinguished Members provide personal accounts of their own lives in physiology. This comprises a sound recording and transcript of an informal interview, and some contemporary photos to complete the item. These interviews are accessible in The Society's archive at the Wellcome Library to scholars as well as Society Members for review. The list of interviewees includes: Horace Barlow, Ron Cook, John Gillespie, John Grey, Otto Hutter, Sally Page, Tom Sears, Ann Silver, Hans Ussing, Wilf Widdas, Roger Woledge, and others. A further half dozen are at the 'final correction' stage. We also have a strong list of current and projected interviewees – not all those on our list will know of it yet!

Our scientific meetings often feature a stand designed by HAC and Members local to the meeting. This might highlight interesting and significant features of the local department. Historic (or at least *old*) items of equipment form a popular feature. With much scratching of heads and general befuddlement, Members try to figure out quite what the device on show used to do (in more competent hands) to further physiology.

Our official archive is held at the Wellcome Library. It comprises of the papers and correspondence of the Committee (now Council) of The Society, minute books, Grey Books, *etc.* There is also a large photographic collection, papers and other items from distinguished former Members. The collection is fully catalogued and available at http://archives.wellcome.ac.uk (use the Reference SA/PHY under the 'Archives & Manuscripts' tab for a comprehensive listing).

HAC administers the Paton Prize Fund. A bursary (up to £1000) can be awarded for travel and incidental expenses associated with work on any aspect relating to the history of major ideas and of the people that have shaped modern physiology. An eminent invited speaker is chosen jointly with the board of *Experimental Physiology* to deliver the bi-annual Paton Lectureship (the 2012 presentation by Jere Mitchell can be seen at www.youtube.com/physoctv).

A perennial question put to HAC concerns items of equipment, some of undoubted historical interest, which have to find a new home when no longer wanted in their 'department'. We have very few options open to us. The Science Museum (for example) will only accept truly historic items, generally those personally associated with scientists of great distinction, such as Nobel Prize winners. So the glorious kymographs, plethysmographs, tambour blood pressure monitors and the rest can remain homeless. Our generic advice is to check with local museums - often at the host institution. At the very least, this might ensure that a competent historian of science can 'triage' the materials on offer. The Society itself has no facilities to store such items. However, we will maintain and refresh a small display in the open areas of The Society's new home at Hodgkin Huxley House. So acquiring some especially interesting kit will be a priority.

View of the main entrance of the ICC from Victoria Square

2013 Forthcoming events

21 April

Fishing with Flies, Worms and Bacteria: Emerging Models for Mammalian Membrane Transport and Trafficking (sponsored symposium at Experimental Biology 2013)
Boston Convention & Exhibition Center, Boston, USA
www.physoc.org/eb2013fishing

23 April

The Neuroendocrine Regulation of the Mammalian Reproductive Axis (sponsored symposium at Experimental Biology 2013)
Boston Convention & Exhibition Center, Boston, USA
www.physoc.org/eb2013neuroendocrine

21 – 26 July

IUPS 2013
The ICC, Birmingham, UK
www.iups2013.org

Will you be attending IUPS 2013?

Don't miss the premier event for the physiological sciences this year!

21–26 July 2013, Birmingham, UK

Denis Noble, CBE FRS, President of the International Union of Physiological Sciences, speaking at IUPS 2009, Kyoto, Japan, said: "Having used molecular biology to break a man down into his tiniest components – his genes, his proteins and all the other molecules – we need to understand how to put all those pieces back together again. This is precisely what physiology is about."

And this is precisely IUPS 2013 is all about, and we are also celebrating our rich history, our tremendous advances and our bright future in furthering our understanding of biological systems.

From the opening lecture being given by Nobel Laureate, Roger Tsien, to the final Plenary by Karl Deisseroth, the International Scientific Programme has secured over 100 symposia (500 speakers), 35 keynote lectures and a raft of extracurricular activities to keep even the most hardened sceptic occupied.

In addition, we will be bringing physiology to the masses, with a public lecture by Russell Foster and three days of exciting, interactive and hands-on activities with the Mobile Teaching Unit, which will be based in the busy Victoria Square in Birmingham city centre.

A range of lunchtime sessions have been scheduled, where participants can explore and learn about things such as effective presentation skills, statistical reporting, publishing, ethics and gender issues in science.

We'll be blogging, tweeting (#iups2013) and 'Facebooking' throughout the meeting, so if you are the social-media type, don't be shy!

By the time you read this article, abstract submissions for IUPS will have closed, but do not fret, whether you are presenting work or not; early-bird registration does not close until 12 April 2013, so you can still register! You simply won't want to miss the broad spectrum of truly world-class science we have scheduled over four and half days. If child-care is an issue don't worry, **Camp Physiology** (our full-day crèche service) is available for all our future physiologists!

Our website is continually updated with all the latest news, so bookmark www.iups2013.org to follow all the action.

Did you know?

- IUPS 2013 incorporates the Joint Meeting of the 27th European Microcirculation Society (hosted by the British Microcirculation Society) and 7th European Vascular Biology Organisation meeting?
- IUPS 2013 replaces the regular annual meeting of both the Federation of European Physiological Sciences (FEPS) and the Scandinavian Physiological Society (SPS)?
- IUPS 2013 marks exactly 20 years since the UK last hosted it in Glasgow in 1993? And before that in Oxford in 1947 as one of the few places not ravaged by the Second World War.
- IUPS 2013 has been almost eight years in the planning? We won the right to host it in San Diego in 2005.
- IUPS 2013 will be at the International Convention Centre, Birmingham, located right in the heart of the city centre, surrounded by bars and restaurants?
- IUPS 2013 will have over 2100 abstracts from 78 different countries?
- IUPS 2013 hopes to attract up to 4000 participants?
- IUPS 2013 currently has over 50 exhibitors?
- IUPS 2013 will be followed by IUPS 2017 in Rio De Janeiro, Brazil?
- That the first IUPS meeting took place in Basel in 1889?
- That the most recent Congress was in Kyoto, Japan in 2009?

BNA2013: Festival of Neuroscience

7–10 April 2013, London, UK

The British Neuroscience Association's biennial meeting in 2013 will be a unique event. Eighteen learned societies with a neuroscience interest, including The Physiological Society, have contributed to the programme, creating a meeting with 56 scientific sessions and eight plenary lectures involving more than 240 speakers, over 80 from outside the UK.

The Society is supporting two symposia:

- *Do glial cells regulate the balance between inhibition and excitation?* Andrew Trevelyan (Newcastle University)
- *Cerebellar contributions to motor, cognitive and emotional behaviour* Richard Apps and Stella Koutsikou (Bristol University)

We are also sponsors of David Attwell's plenary lecture *CNS White Matter: The role of neurotransmitter signalling to oligodendrocytes and their precursors in health and disease.*

The hottest topics in neuroscience research will be covered under eight themes: Development; Molecular; Cellular and Synaptic Mechanisms; Sensory and Motor Systems; Cognition; Circadian, Homeostatic and Neuroendocrine Mechanisms; Nervous System Disorders; Methods and Techniques; and Public Awareness and Societal Impacts. Over 900 abstracts representing all aspects of the subject have been submitted.

A major public engagement programme will form part of the Festival of Neuroscience – enabling members of the public to interact with scientists, carers, charities, funders, policy-makers and some well-known celebrities with experience of mental health issues, to learn more about the brain and the importance of a multi-disciplinary approach to research.

Society Members benefit from a discounted registration fee. See www.bna2013.com.

Workshop at the 2011 Festival of Neuroscience. From left to right: Barbara Sahakian, BNA President David Nutt, Colin Blakemore and Lord Willis of Knaresborough.

Patrick Seale, University of Pennsylvania, delivers a lecture on transcriptional control of brown adipose development.

Meeting Notes

Metabolism & Endocrinology Themed Meeting

Brown adipose tissue: a new human organ?

11–13 December 2012, London, UK

Shalini Ojha, Helen Budge & Michael Symonds

University of Nottingham

Run by The Physiological Society, in partnership with the Academy of Medical Sciences, this meeting was held at The Royal Society and organised by Antony Vidal-Puig, Jan Nedergaard and Michael Symonds. It covered the subject from a multi-disciplinary standpoint, with focus on endocrinology, development and ageing, appetite and metabolic control, tissue imaging and thermoregulation.

Obesity is increasing at epidemic proportions and brown adipose tissue (BAT), with its role in body metabolism and energy expenditure, may provide one means of attenuating the growth of this problem. The meeting brought together leading researchers from across the world to discuss the recent advances in BAT research. BAT has emerged as a possible human organ with potentially a significant role in energy balance.

BAT is a thermogenic organ. In contrast to white adipose tissue, the primary function of BAT is to produce heat by the process of non-shivering thermogenesis. This process is enabled by the presence of a unique protein, uncoupling protein 1 (UCP1), which uncouples substrate oxidation from ATP production, releasing the energy liberated through oxidation directly as heat. The emergence of BAT in the forefront of metabolic discussions is fuelled by its recent (re)discovery in adult humans. The role of BAT in metabolism and energy balance was discussed, including new insights into physiological methods and pharmacological agents that can recruit BAT. For example, a role of BAT in diet-induced thermogenesis is highly controversial, and some new findings were presented which support the case for BAT involvement. These included human studies using thermal imaging and positron emission tomography combined with computed tomography (PET-CT) that demonstrated some evidence to support activation of BAT in response to meals.

Delegates enjoy the Society Dinner at The Churchill War Rooms.

The recent increased interest in brown-in-white or BRITE cells was discussed, and the meeting highlighted the role of several new transcription factors such as early B-cell factor 2 and other regulatory mechanisms involved in BAT physiology and its role in energy balance. At present, PET-CT scans remain the gold standard of imaging BAT, and recent data presented demonstrate that thermogenic responses decrease with age and that BAT activity is enhanced by cold acclimation and significant reduction in body mass index following bariatric surgery. Thermal imaging is a non-invasive and cost effective alternative modality for BAT imaging, and findings presented demonstrated the effects of mild cold exposure, diet and body mass index on the supraclavicular depot of BAT in humans. Other imaging modalities discussed include the use of magnetic resonance imaging in humans and experiments showing the delivery of lipophilic nutrients to brown adipocytes using superparamagnetic or fluorescent nanocrystals.

The role of BAT as an endocrine organ was also discussed. It is being recognised that BAT may have some role as a producer of hormones (e.g. triiodothyronine) and signalling molecules such as retinol-binding protein 4, which modulates insulin resistance and glucose metabolism, and adipokines such as interleukins and insulin-like growth factor and fibroblast growth factor. The involvement of BAT in lipoprotein metabolism was demonstrated by findings demonstrating the high uptake of lipids from lipoprotein by brown adipocyte.

It was apparent from the meeting that BAT research is entering a new exciting and dynamic phase which was highlighted by the advances currently being made. These studies have potential to produce translational research for the prevention and treatment of obesity and associated metabolic conditions.

An undergraduate experience

Caroline Bull

3rd year Human Physiology BSc student, University of Leeds

The opportunity to attend the recent Metabolism & Endocrinology Themed Meeting was granted to me as a recipient of The Physiological Society's early careers bursary. As a third year undergraduate this was an invaluable experience, not least to experience the environment of a professional conference, but also because of the topic, and the excitement surrounding the field of brown adipose tissue.

It was an honour to communicate with researchers of such calibre and to be able to put faces to names behind papers that I had come across in the literature. I enjoyed stretching my knowledge in order to understand the different experimental techniques and approaches outlined by the speakers. The work discussed by Alexander Bartelt of The University Medical Centre, Hamburg- Eppendorf stood out as particularly elegant. I also found the presentation by Michael Symonds of Nottingham University detailing the development and role of BAT in early life engaging.

The researchers' enthusiasm was central to the meeting and it was great to experience this atmosphere as an undergraduate hoping to pursue academia in a similar field. A highlight of the meeting was Francesc Villarroya describing the understanding of BAT as 'sexy science', a statement that greatly contradicted the nature of family and friends' reactions when I mentioned that I was attending a conference on brown fat!

The conference dinner, hosted at the Churchill War Rooms was thoroughly enjoyable and appropriate to show the international attendees of the conference the charm of London. Having had such a positive experience at my first conference with The Physiological Society, forthcoming conferences have a lot to live up to!

Meeting Notes

Biophysical Society's 57th Annual Meeting

2–6 February 2013, Philadelphia, USA

Sally Howells & Nick Boross-Toby
The Physiological Society

Philadelphia greeted us with snow flurries and a biting wind, but we soon found shelter in Reading Terminal Market and filled up on some tasty local produce that gave us the strength to set up the exhibition stand. The exhibition hall was open for three days, during which time we ran a prize draw and were involved in a scavenger hunt made for high school students. We also offered delegates the chance to discuss their research during 'meet the Editor' sessions with Editor-in-Chief David Paterson, Deputy Editor-in-Chief Hiro Kubo, and Reviewing Editors Donald Bers, Derek Bowie, Peying Fong, Mike Sanguinetti and Richard Vaughan-Jones.

The meeting was well attended with over 5800 delegates, and many people were interested to learn about the history of the journals and The Society.

David Paterson said, "*The Journal of Physiology* has traditionally been the home for biophysics research, so it's exciting to be able to promote *The Journal* to the delegates and remind them that it is an ideal outlet for their papers. I hope that as a result of attending this meeting, we will see an increase in submissions of top-quality biophysics papers."

There were a number of representatives from the Editorial Board at the meeting; we all got together to evaluate the success of the meeting and discuss future developments and the direction of *The Journal*. We have already started planning for the next meeting in San Francisco, 2014.

Nick Boross-Toby and Sally Howells at *The Journal* stand.


The meeting welcomed nearly 6000 delegates.

Throughout the meeting we played the filmed interviews of Consulting Editors Bert Sakmann, Frances Ashcroft and Peter Hunter, as well as showing slides on the reasons to publish with *The Journal of Physiology* and *Experimental Physiology*. Delegates were particularly impressed with our free virtual issue of papers of particular relevance to biophysics. We were also pleased to be able to promote the new open access journal *Physiological Reports* and meet with Editor-in-Chief, Sue Wray, at the stand.

We were delighted that Consulting Editor Dame Carol Robinson was here to receive the Anatrace Membrane Protein Award and acknowledged *The Journal* in her talk 'Mass Spectrometry – from peripheral proteins to membrane motors'.

Overall the meeting was a great success, and we are looking forward to the 58th Annual meeting in California – hoping that that too will coincide with the Super Bowl!

Meeting Notes

The Turkish Physiological Society Meeting 2012

25–29 September 2012, Trabzon, Turkey

Rodríguez Arellano
University of the Basque Country, Spain

David Carpenter
University of Albany, USA

Graham Dockray & Andrea Varro
University of Liverpool, UK

Roderick Scott
University of Aberdeen, UK

Alexei Verkhratsky
University of Manchester, UK

In the last week of September, 300 members of the Turkish Physiological Society and a group of foreign guests met in Trabzon. The meeting was held at Karadeniz Technical University which has spectacular conference facilities and exceptionally comfortable accommodation with views over the Black Sea. The University, founded in 1955, stands in attractive extensive woods on slopes which climb steeply from the sea.

The meeting was hosted by Ahmet Ayar, the Head of Physiology at the university, and his expert team. Physiology research and teaching are increasingly well supported in Turkey and considerable investment has gone into buildings, infrastructure and training across the country. Clear strengths have emerged and include the study of epilepsy, obesity, exercise physiology (particularly in the context of health), therapeutic aspects of cannabinoids, peptide neuroendocrinology, the physiology of reproduction, diabetes research and the study of reflex mechanisms.

The visiting guests presented research on diverse topics, including, 'Are fish safe to eat?', 'Making sense of gut–brain signals', neuroglia in health and in Alzheimer's disease, microenvironment regulation by myofibroblast and actions and potential applications of pore-forming sponge toxins. Some of the work presented was from ongoing research collaborations between Turkish physiologists and their visitors.

The scientific sessions were punctuated with posters and great hospitality. A fine introduction to the culinary delights of the Black Sea, Trabzon and surrounding area was generously provided, with guests enjoying a dinner hosted by Ahmet Kalkan (Dean of the Graduate School of Health Sciences at Karadeniz Technical University). We were also very kindly given some gastronomic gifts, including the most delicious hazelnuts grown on the hills around Trabzon. In addition to the scientific program, very exciting cultural trips were organized to the lake at Uzungöl with its mosque and Sumela Monastery. There was even an opportunity to dance to the wild rhythms of Black Sea music. We really got a clear impression on our travels of how, historically, this area was isolated from the Anatolian interior by a wall of mountains which skirt the Black Sea. Today, there is an international feel to Trabzon with its airport, thriving university and dynamic city.


The campus of Karadeniz Technical University.

The medicalization of inactivity

The physiological impacts of our increasingly sedentary lives have been widely studied in recent years, creating a leap in both our understanding of the processes within our bodies and public interest. Does the mountain of evidence accrued support treating inactivity as a medical issue?

Michael Joyner

Jill Barnes

Department of Anesthesiology, Mayo Clinic, USA

Physical inactivity now rivals smoking as the leading cause of 'preventable' deaths in the developed world (Lee *et al.* 2012). Additionally, physical inactivity-related mortality is rising rapidly in the developing world. These observations have led to questions about whether physical inactivity should be viewed as a separate medical diagnosis or even a medical condition (Chakravarthy, Joyner & Booth 2002; Joyner 2012). Taking it a step further, it might also be possible to 'split' a physical inactivity diagnosis into two parts: primary deconditioning which is just too little physical activity and too much sitting around; or secondary deconditioning as result of inactivity caused by some other medical condition – for example, enforced bed rest during certain complications of pregnancy, bed rest associated with infectious disease, or reduced activity due to orthopedic injuries.

Activity and inactivity versus fitness

Before going further in this discussion it is important to distinguish between physical activity or inactivity and physical fitness. Many studies looking at the relationships between activity or inactivity use questionnaires or tracking devices like pedometers to get some idea about the total amount of activity people get per day. This activity is then estimated to be light, moderate or vigorous. Analysis of this data can then be framed in the context of activity or inactivity with some estimate of exercise intensity (Troiano *et al.* 2008). For many years the discussion was mostly about activity as an experimental intervention and the inactive state was considered the 'normal control condition' or frame of reference. In recent years this has changed, primarily as a result of the thinking of Frank Booth and colleagues who have pointed out that humans were designed to be active and that our cultural and genetic heritage as hunter-gatherers and traditional agriculturalists included high volumes of a wide range of physical activity (Chakravarthy & Booth, 2004). Thus came the idea that the active state is the physiologic norm and the inactive state should be seen as the intervention or deviation from normal (Booth, Laye & Roberts, 2011). This idea has exploded in the popular press and it is interesting to note that, for a number of rodent models that have what might be broadly described as metabolic diseases, the disease phenotype of interest is prevented or attenuated when the caged animals are given access to voluntary running wheels (Brown *et al.*, 2012; Engber, 2011; Park *et al.*, 2012; Rector *et al.*, 2011). So the question is: have we been studying the condition of primary physical inactivity instead of the disease of interest?

Credit: Chris Johnson.

Michael Joyner instructs students on cardiovascular testing in the exercise physiology lab.

"Primary inactivity is a risk factor for hypertension diabetes, and may extend to cancer and dementia: Isn't it a medical condition deserving of an independent diagnosis?"

Some studies have also looked at death and disease rates versus varying levels of cardiorespiratory fitness typically determined by a graded exercise test on a treadmill providing an objective measurement of fitness. In general, people who are highly active will have greater cardiorespiratory fitness than less active individuals, but high cardiorespiratory fitness can theoretically be achieved by relatively limited periods of vigorous intensity exercise, in the absence of large volumes of physical activity. The point is that physical activity and fitness, while usually related, are not synonymous.

Activity, inactivity, heart disease and death

Exercise is perhaps best known as being protective against cardiovascular disease. Data from numerous population-based studies suggests individuals that have some combination of either high daily physical activity or greater levels of cardiorespiratory fitness (as noted above, they are not exactly the same thing) have much lower all-cause mortality (Barlow *et al.*, 2012; Berry *et al.*, 2012; Moore, 2012). People in the highest categories of physical activity and fitness typically have cardiovascular mortality rates that are about 50% of that seen in the general public as a whole. From a public health perspective, many of the benefits of exercise begin to accrue as people move from the least active categories to the moderate levels of physical activity. Figure 1 shows the relationships between physical activity levels, rates of mortality and years of life gained. For many years this reduced mortality was seen as primarily due to the fact that exercise had powerful effects on traditional cardiovascular risk factors. For example, exercise lowers blood pressure, improves blood lipids, and has powerful anti-diabetic effects. However, when the effects of exercise on traditional risk factors for cardiovascular disease are looked at in total, only about 60% of the risk reduction is accounted for (Mora *et al.*, 2007). This means that 40% of the protective effects of exercise might be described as 'physiological dark matter' (Joyner & Green, 2009).

Hints about 'physiological dark matter'

There are a few obvious candidates for the as-yet unexplained protective effects of exercise. First, high levels of physical activity and/or structured exercise training have profound effects on the autonomic nervous system and these might be generically described as 'pro-vagal' and would tend to protect individuals from arrhythmias (Billman, 2009). Exercise also has preconditioning-like effects on the cardiac muscle which would be protective against myocardial infarction and other cardiac problems (Powers, Quindry & Kavazis, 2007). Exercise training and physical activity also improve endothelial function, which is both anti-atherogenic and anti-thrombogenic, both of which would be protective against cardiovascular disease (Green, 2009). Individuals who participate in prolonged intense exercise have larger coronary arteries and structural remodeling associated with the exercise might also in fact be protective (Nguyen *et al.* 2011). Finally, exercising muscle also secretes a number of myokines that have potent anti-inflammatory and anti-diabetic effects (Pedersen & Febbraio 2012). From a physiological perspective these adaptations, generally associated with increasing cardiorespiratory fitness, would all be protective against heart disease.

Physical activity as an independent risk factor for cardiovascular disease

Is physical inactivity (or lack of cardiorespiratory fitness) a risk factor? One way to look at this is to consider data showing the relationship between all-cause mortality and/or traditional risk factors and physical activity or cardiorespiratory fitness. In a classic study from the mid-1990s, Blair and colleagues demonstrated that individuals with high levels of traditional risk factors who also had high cardiorespiratory fitness scores had only minimal increases in risk as a result of these additional factors (Blair *et al.* 1996). By contrast, the risk factors showed what might be described as their full expression only in the least fit individuals. Additionally, risk was increased in the least fit people with relatively low traditional risk factor scores and more recent data has confirmed this idea (Barlow *et al.* 2012). These types of data and subsequent analysis suggests that physical inactivity and the associated lack of cardiorespiratory fitness are in fact independent risk factors for cardiovascular disease and all-cause mortality. Some might argue this is semantic hair-splitting, but if you accept that fact that primary inactivity is a risk factor for hypertension diabetes, and may extend to cancer and dementia, then isn't it a medical condition deserving of an independent diagnosis?

Adverse responses to exercise training?

One interesting idea about the protective effects of exercise that seem to be independent of traditional risk factors, is the observation from large training studies that at least some individuals might be described as adverse responders to exercise training (Bouchard *et al.* 2012). This means that their blood pressure rises in response to training, their lipids get worse, or perhaps their blood glucose increases. Typically, adverse responses are seen for only one risk factor and do not cluster in the same person. That having been said, are these individuals in fact adverse responders to exercise? Are the protective effects of exercise that seem to be independent of traditional risk factors also somehow also 'not responding' to exercise training? Are there other lifestyle-related behaviors that may explain the seemingly counterintuitive response to exercise? These are important questions about what might be described as 'surrogate markers' for effective

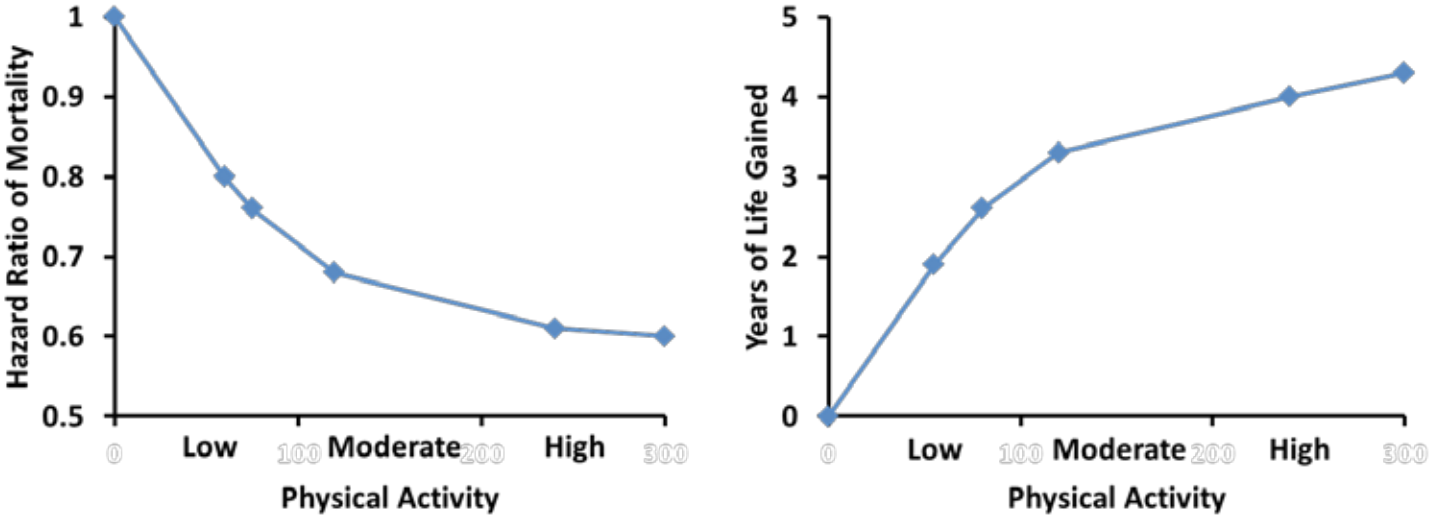


Figure 1. Pooled data on physical activity mortality and life expectancy from ~650,000 subjects enrolled in the US National Cancer Institute Cohort Consortium. Going from no physical activity to the equivalent of ~75 minutes of brisk walking (low physical activity) per week caused a marked reduction in mortality and increased life expectancy by nearly two years. The most active subjects exercised the equivalent of about 450 min of brisk walking further reduced mortality and added four plus years to life expectancy. Figure adapted from Moore *et al.* 2012.

"40% of the protective effects of exercise might be described as 'physiological dark matter'"

exercise interventions designed to improve both individual health and public health in general. In other words, do we tell people who do not have improvements in their traditional risk factors, or in fact have 'adverse' changes in their traditional risk factors, that they shouldn't exercise? Are we in fact denying them the benefits of the significant but less well understood positive effects of exercise?

New ideas about sedentary behavior

High levels of physical activity or cardiorespiratory fitness are protective in terms of all-cause mortality, especially cardiovascular mortality. However, it also appears that bouts of intensive exercise followed by sedentary behavior the rest of the day can be problematic. Additionally, recent evidence clearly demonstrates that going from 'normal' levels of activity to very low levels of physical activity has extremely negative consequences on metabolic regulation in humans (glucose homeostasis) in a matter of a week or so (Olsen *et al.* 2008). All of this would seem to suggest that a combination of relatively intense leisure time physical activity (sufficient to increase cardiorespiratory fitness) and low-grade physical activity throughout the day are probably an optimal pattern to maximize the health benefits of exercise and physical activity.

Exercise and healthcare costs

The data on physical activity and mortality are convincing. How do the data on physical activity relate to healthcare use or healthcare costs? The literature on this topic is much less robust than the literature on mortality. It also suffers from the problem that it is generally cross-sectional in nature and questions about 'nature versus nurture' often arise. For example, perhaps only the most robust and healthy individuals began to exercise in the first place and this confounds the interpretation of cause and effect. One excellent study from the United States on more than 40,000 older individuals on the Federal Medicare Program demonstrated that the most active individuals had yearly healthcare costs that were about 20% lower, and that was also true for the most active obese patients in the study (Wang *et al.* 2005).

Do exercise interventions work?

Exercise interventions clearly improve fitness and risk factors in the vast majority of people who undertake them. However, one of the ideas behind inactivity as a medical diagnosis is that while interventions work, they are hard to implement and people do not stick with them. Additionally, it is unclear how well public education campaigns are working. The number of people meeting physical activity guidelines for health is also incredibly low (Troiano *et al.* 2008). So, could this be improved if inactivity or deconditioning becomes a medical diagnosis complete with an exercise prescription? It is relatively straight forward for a middle-aged person with hypertension, diabetes, or high cholesterol to visit their physician and be given a prescription for drugs that can conveniently be obtained at the local pharmacy. There exists cultural, commercial and governmental infrastructure to support

"The most active individuals have yearly healthcare costs that are about 20% lower than average"

this approach to disease management. What if it were that easy for a physician to send someone to the gym or tell them to go for a walk? Would it work? The data to date are not convincing one way or the other, but probably deserving of serious study (Pavey *et al.* 2011).

Lessons from smoking

Smoking rates have declined in many countries and at least some of this has been due to active intervention and advice by physicians. However, other public health strategies such as making cigarettes less available to young people and higher taxes have probably done more to reduce smoking rates than people being urged to quit, or being enrolled in smoking cessation programs (CDC 2007). The smoking experience suggests that a combination of approaches will be needed to promote physical activity out in the real world. These approaches will likely include a combination of public health initiatives (education), government initiatives (public places promoting physical activity), and medical initiatives (low-cost access to supervised exercise intervention programs, insurance deductions for participation). However, another important aspect to the declining smoking rates may be the societal shift on acceptability. It is often viewed as distasteful, for example, to smoke in most public indoor spaces. In terms of physical inactivity, we have not reached the tipping point for social preference.

The role of society

If large-scale public health initiatives demonstrate varying results, what roles do individuals play in initiating such change? In particular, what role do social networks have in promoting healthy behaviors? Recently, Li *et al.* (2012) discussed the use of social media as an intervention tool to prevent childhood obesity. In addition, others have used statistical approaches to document how behaviors, such as weight gain or alcohol use, spread throughout a social network (Christakis & Fowler, 2012). These innovative techniques may reveal much about initiating positive health behaviors and using social media to promote the idea that an active lifestyle is the healthy norm.

Conclusion

Physical inactivity is a major cause of disease and the effects of exercise on morbidity and mortality are at least partially independent of so-called traditional risk factors. These observations justify the position that physical inactivity (and deconditioning) should be viewed as an independent medical diagnosis amenable to prevention via public health measures and treatment via the medical community.

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Are we in control of our own health?

If you take up jogging, will you live longer? Or will it just feel longer? Our limited understanding of genomic and epigenomic factors may be preventing us from finding the truth.

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Most readers of this article would support the belief that our 'genes' interact with a variety of environmental factors, such as nutrients and physical activity, to shape our health and risk of chronic disease. Indeed, this basic premise dominates the research fields of ageing, cancer, cardiovascular and metabolic disease. Yet it is very rare indeed that a direct causal connection between a particular 'behaviour' and a health outcome has been established. Equally, the number of established links between a specific DNA sequence and any of the major multifactorial chronic disease states is limited.

There are numerous unknowns when it comes to the validity and application of high throughput genomics being used to help us understand how our genes impact on our disease risk. We need to ask the question, is it possible to genuinely embrace modern evidence-based medicine when scientists with no multidisciplinary training manage the multidisciplinary science? Technical limitations within data-sets are unappreciated, and no common minimum acceptable level of 'evidence' to enable evidence-based medical practice is established.

This article addresses some of the barriers to advancing the contribution genomic and epigenomic technologies can make to our understanding of human health and physiology. What I want to know in the end, is, if I take up jogging today, and do my 150 minutes a week, every week, like a good citizen, will I live a healthier and longer life? Or will it just feel longer?

Lifestyle modification has been shown to improve the group incidence of type II diabetes in intervention trials, but no robust exercise-only interventions have been carried out. So it would be easy to focus on risk-factor modification and not give due care and attention to the fact that these behaviours are not necessarily causal for future disease risk. In fact, the available intervention data demonstrates that lifestyle modification involving exercise training does not reduce the incidence of major cardiovascular events (such as myocardial infarction) at all, though it does reduce the incidence of diabetes and modify other important risk factors (Wing, 2010). The significant healthcare costs and levels of morbidity associated with cardiovascular events are presumably what justified the costs of the studies in question.

If our genes haven't changed it must be the environment, right?

In a recent meta-analysis, Lee and colleagues conclude, "the association of lung cancer with smoking is strong, evident for all lung cancer types, dose-related and insensitive to covariate-adjustment. This emphasises the causal nature of the relationship" (Lee *et al.* 2012). While it is rather insensitive to label

the discipline of epidemiology (addressing any topic) as 'largely' correlational, what we can reflect on is that the relative risk of developing lung cancer from smoking ranges from <2 up to >40-fold increase. The risk also appears to vary from continent to continent, perhaps reflecting differing genetics (but also data recording methodologies). Put bluntly, one of the most accepted truisms in evidence-based medicine interacts with other strong factors, including genetic predisposition, to *dramatically* determine the risk to the individual.

Is the successful identification of a strong link between cigarette-smoking and lung cancer proof that epidemiological methodology is a valid synonym for 'evidence-based medical research', or is it an exception? A number of scientists have recently made the rather perplexing statement that low physical activity is the 'new smoking'. The American College of Sports and Medicine has launched an initiative called 'Exercise is Medicine', trade-marking the name in the process! Meanwhile, numerous academics have extensively documented the claim that 'exercise' offers a cure to almost all known chronic disease states (Pedersen & Saltin, 2006), a mantra unquestionably repeated by others (Booth & Laye, 2010). If true, where is there room for genetic or familial influences – influences that have been established in supervised intervention studies in humans (Bouchard *et al.* 1986; Oppert *et al.* 1995)?

The truth about exercise is that there are very few examples of properly controlled human intervention trials that have measured a reduction in disease, a topic I explore in greater detail online (Timmons, 2012). What we do have is extensive evidence that exercise, as part of an overall lifestyle modification strategy, modifies 'risk factors' for poor health and chronic disease. To address the question "Are we in control of our own health?", we must progress with caution through the minefield of epidemiological evidence, and ask honestly whether *any* existing evidence reaches a level of confidence sufficient to interfere with an individual's behaviour choices. To draw analogy, the basis for the strongly held views on the causal benefits of increased physical activity would be like basing the conclusion that cigarette-smoking causes lung cancer because both are associated with 'coughing'. Nevertheless, smoking will almost certainly get you some other way, e.g. chronic obstructive pulmonary disease.

Variation is a physiologist's new best friend

Firstly, most interventions that I am aware of (except prolonged anoxia!), result in a variable outcome in outbred mammals, with marked inter-subject and inter-study heterogeneity. This is true in drug trials and true in studies of the impacts of exercise or lifestyle modification. Such variation has been unintentionally overlooked through a focus on group average responses (or actively denied by some too attached to their pre-existing beliefs). This biological variation is also considered the 'enemy' of the research scientist, creating concern over whether a study may be inadequately powered to reveal a 'significant' effect from the intervention. I would argue that, in many cases, the mean effect of an intervention is meaningless to the individual, and thus so are those misguided grant-review questions on power calculations. The key feature of a quality human physiology study, moving forward, will be independent replication of the observation and not power to detect a mean effect.

It is also known that the impact of exercise training on health biomarkers, after supervised intervention, varies dramatically and, for most people, an *adverse* change in a health biomarker will also occur (Bouchard *et al.* 2012). Thus, if you have elevated blood pressure and you have an adverse blood pressure response to a one-size-fits-all exercise regimen, then it is very clear Exercise Cannot Be Medicine (™!). If you have elevated blood glucose levels and you become *more* insulin resistant with exercise training, then physical activity is not "a drug for people with type 2 diabetes" (exerciseismedicine.org). Generalised advice on exercise prescription (in the absence of a valid personalised plan for the individual) is not only unscientific, it could in some circumstances be irresponsible.

Can we use genomics technologies to solve this public health challenge? Well, certainly not if we propose that everyone does 5 hours of power walking (Karstoft *et al.* 2013), rather than 3–10 minutes of sprint interval training per week (Metcalfe *et al.* 2012; Gillen *et al.* 2012) as the majority of humans don't value perpetual motion nor have we undergone such behaviour at any time in our history.

Which flavour of 'omics' will deliver progress?

Assuming common sense is applied, then it will be the integration of new technologies to study human variation – requiring multidisciplinary groups to come together and effectively communicate the limitations of all methods being employed – that will make progress. There is little point perfecting the determination of gene sequence or DNA methylation, with high fidelity, only to correlate it with unreliable plasma glucose samples, or not include the appropriate time control in your study (Barrès *et al.* 2012). To understand why humans respond to exercise training to a highly variable degree, human physiology experts have come together with genomics and systems biology teams (Timmons *et al.* 2012). Currently, the physiological journals do a rather poor job when it comes to the evaluation of studies utilising systems biology tools, preferring to question the basis of such research (Timmons, 2011).

To progress evidence based medicine, we need to train individuals in multidisciplinary research. It is not sufficient to put together some esteemed colleagues from distinct fields (Turan *et al.* 2011) – without a comprehensive appreciation of obvious biological or clinical covariates by all parties no progress can be made. Modelling suboptimal 'omic' data can do much damage, as the lack of quality of the clinical data (Mootha *et al.* 2003) is often put to one side, especially in so-called high-impact journals. Thus, the first breakthrough required is not a technology platform, but a more sustained effort to train numerically-confident physiologists with an interest in computer science, genomics and big data, and put to one side academic debates about physiology versus systems biology.

Will nucleic acid sequence-based analysis provide the genomic tools for future physiological studies? To date, it has only been possible to unveil a small number of variations in the human genome that determine the outcome of physical activity. These include stable sequence related variations in nucleic acid content that predict the gains in aerobic fitness gained from exercise training (Bouchard *et al.* 2011) and variations in the abundance of a set of RNA molecules which do not vary by muscle activity (Timmons *et al.* 2010), but rather are set to a pre-exercise level by mechanisms not fully established (some link to DNA variants while others may be epigenetically regulated).

"The truth about exercise is that there are very few examples of properly controlled human intervention trials that have measured a reduction in disease"

This was the first example in human physiology where a mathematical classification model (www.medicalprognosis.com) was used to mine RNA transcriptomic data sets to then select genomic loci for targeted genotyping to yield a new diagnostic (www.XRgenomics.co.uk). I feel this is an important example where human physiology and 'big science' methods have been combined to produce progress beyond that which has been achieved with genome-wide DNA screening epidemiology. In the genome-wide genotyping studies, limited clinical phenotyping almost certainly rate-limits progress. By using data integration methods, analysis can be applied to hundreds, rather than thousands, of samples, making intervention studies affordable. What is now required is larger scale cooperation across the human physiological community to create 'pools' of high-quality human physiological data sufficient in size to carry out this type of molecular epidemiology.

The EU FP7 project, Metapredict, is one example, where more than 10 teams have come together to share existing data and generate biological materials and physiological data on over 1500 humans (www.metapredict.eu). This study will integrate a variety of 'omic' technology to produce novel diagnostics for blood pressure, aerobic fitness and glucose tolerance responses to supervised time-efficient exercise training (<10 mins per week). Based on these integrated studies we should be able to utilise DNA, RNA and metabolite profiles to predict which health biomarkers are going to be positively modified in the individual, using a blood sample, DNA swab or micro-tissue biopsy. We are applying these strategies to a variety of interventions, including an intervention that overcomes societal limitations of current public health advice (i.e. a perceived lack of time). Indeed, the laboratories of Kraus and Kujala have made some excellent progress, discovering metabolite signatures that co-vary with clinical status (Shah *et al.* 2009; Kujala *et al.* 2013). The next step is to prove they are predictive of future events and integrate such data into multi-'omic' models.

A very trendy term is emerging in the literature to explain what can't be explained by sequence-based inheritance. That term is 'epigenetics'. If you don't understand something, then it's definitely epigenetic modification in action! The mysterious little bioactive RNA molecules (Gallagher, 2010; Davidsen *et al.* 2011) called microRNA's, are highly abundant products of longer RNAs and, in turn, 'genes', which are produced by a process analogous to any protein. Bizarrely, they are frequently listed as mediators of epigenetic action, highlighting the general level of mystery around both concepts – they are just ordinary genes, doing an ordinary job, at the RNA level. In the past year, epigenetic analysis of human muscle tissue has yielded claims of both importance and surprising plasticity in the 'stable' DNA modification that one can detect in human cells (Barrès *et al.* 2012). It is rather surprising that a single bout of exercise can 'modify' your DNA (as the press release suggested). The truth is that the genes profiled switch on and off with circadian pattern in the at-rest human (Vissing *et al.* 2005) and this, more than anything, highlights the extreme dangers of poor peer-review and candidate-based analysis. If a global analysis of transcriptional events had been coupled with a global and detailed map of methylation, the results would not have been nearly as newsworthy. There remains to be a technically valid and scientifically robust study of epigenetic regulation in human muscle and the impact of exercise and lifestyle.

To pursue this correctly, the theme mentioned above is critical. You need to assemble a multi-disciplinary team with a genuine understanding of physiology, bioinformatics, statistics and DNA biochemistry (for example, I've never had a clear answer to the question, how do you isolate DNA from muscle tissue and ensure epigenetic events are captured?). Never has physiology been so important, and yet never has fashion-driven technology so dominated biomedical science. Fifteen years after the emergence of gene-chip technology for global RNA profiling, my laboratory still

works with the technology and we are still discovering better ways to use the technology and data. Grant reviewers still attempt to force us to move to next-generation sequencing of RNA, a technology that does not yet work reliably (Hansen *et al.* 2011).

Conclusions

Why have the epidemiological predictions failed us on the impact of lifestyle modification and the link between diabetes and cardiovascular disease? The truth is, they haven't. There was abundant data that hyperglycaemia is not a strong predictor of macrovascular disease in the UKPDS analysis, while beneficial effects on microvascular disease were predicted. Sadly, the details are being ignored by many in favour of a good simple headline – "Exercise prevents cardiovascular disease by preventing type 2 diabetes". Politically-correct thinking is driving a public health strategy and that now needs revision. Other researchers are still attempting to evaluate high-volume organised physical activity (Beck-Nielsen *et al.* 2012), a behaviour that modern humans dislike and a behaviour that humans probably never exhibited, given the energy–transfer efficiency of food into locomotion. Think about it; why would we move around all day 'chasing after' food, as surely there is no faster route to the eventual extinction of a species and its habitat, through excessive consumption. It's also an effective strategy for increasing the carbon footprint of humans on this planet!

So how do we combine the latest 'omic' developments to advance this area of public health? Firstly, what we need is exercise-only intervention studies, using modes of exercise that are likely to overcome real-world barriers and that are genomic-driven, tailored to the individual. Also, as most studies apply one-size-fits-all exercise intervention plans, we need strategies to overcome the limitations of such studies using individualised diagnostics. In that way the individual's outcome, for each major health parameter, can be re-evaluated on the basis, for example, of their 'omic' responder status. Only then will we edge closer to the truth about exercise.

"The breakthrough required is not a technology platform, but to put to one side academic debates about physiology versus systems biology"

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Films, muscle, potassium and exercise

David Jones recounts his quest, triggered by a 1970s movie scene, to find out why potassium is bad news for skeletal and cardiac muscle, yet good news for many other aspects of our physiology.

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Back in the 1970s I used to go to the cinema pretty frequently. One of the best of the actors of the time was George C Scott. Scott is better known as General Patton, in the film of that name. However, it is a little known film called The Hospital that is relevant here. The film is a very black comedy in which Scott plays Dr Bock, who has problems with his marriage, on top of which there is a series of murders of patients in his care. Things get so bad that Dr Bock is driven to contemplate suicide and there is one scene in which he is sitting with a tourniquet around his arm about to inject himself with a syringe full of potassium chloride. He doesn't do it, and I can't remember now what distracted him, possibly Dianna Rigg, his exceptionally attractive co-star, but I do remember sitting in the cinema thinking, "Why is KCl going to kill him?" After all, potassium is the major intracellular cation, it is found in nice things like fruit juices and bananas, and, surely drinking too much fruit juice isn't going to kill you? By coincidence, this question, and the role of potassium in muscle and exercise physiology, was going to crop up at regular intervals over the next 40 years.

At that time I had just started working with Richard Edwards and David Hill at the Royal Postgraduate Medical Centre, Hammersmith Hospital, next door to Wormwood Scrubs prison. Richard had recently introduced the muscle biopsy technique into this country and he and David Hill were beginning to measure strength and function of human muscle, both of normal subjects and patients with a variety of muscle problems, and I was lucky enough to join them at the start. We were also very lucky that Brenda Bigland-Ritchie came to work with us while on a sabbatical year and we set about the most enjoyable part of any research project – just playing about and seeing what happens, but with a general interest in muscle fatigue.

One of the first things we noticed is that when stimulating the adductor pollicis muscle it is necessary to use a relatively high frequency of 80–100 Hz to obtain maximum force, but the muscle then rapidly fatigues. If a lower frequency is used, say 20 Hz, there is initially a lower force but the force is then maintained (Fig. 1). These experiments were carried out with the blood supply to the arm occluded with a tourniquet and the explanation seemed fairly obvious; with the high frequencies and high forces energy was being used up very rapidly, while with the low-frequency stimulation the energy reserves were lasting longer. However, as part of the general messing around, we tried changing the frequency during the high frequency stimulation at a time when the muscle was considerably fatigued and, to our surprise, reducing the stimulating frequency resulted in a rapid recovery of force. If the reason for the loss of force was the depletion of an energy reserve, say phosphocreatine, or the accumulation of something nasty, say lactic acid, then there would be no reason why

simply reducing the stimulation frequency in an ischaemic muscle would result in an increase in force. So rather than this behaviour being explained by metabolic changes affecting the interaction of actin and myosin, it seemed more likely that some change in the electrical properties of the membrane was involved. At the time there was interest in the possibility of failure at the neuromuscular junction during fatiguing contractions and this might have been the explanation since we were stimulating via the motor nerve.

Transmission at the neuromuscular junction depends on the release of acetyl choline from synaptic vesicles and it is easy to imagine that when stimulating at high frequencies the rate of release outstrips the ability of the nerve ending to take up the choline, re-synthesise the acetyl choline and package it into new vesicles; reducing the frequency would thus give the nerve ending time to catch up. The test of this was to stimulate the muscle fibre membrane directly rather than through the nerve and neuromuscular junction, but this is difficult and painful to do with human muscle *in situ*. However, I had set up an isolated mouse muscle preparation where it was possible to block the neuromuscular junction with curare, which binds to the acetyl choline receptors, and stimulate the muscle directly with large plate electrodes. For no very good reason we did not believe the neuromuscular junction was the problem, so, to our delight, we found that this isolated, curarised, preparation behaved in exactly the same way as the human muscle, strongly suggesting that the problem lay with the electrical properties of the muscle fibres themselves, not the neuromuscular junction. This was further supported by EMG records from the human muscles where it was clearly seen that the action potential failed rapidly during high frequency stimulation and did not simply

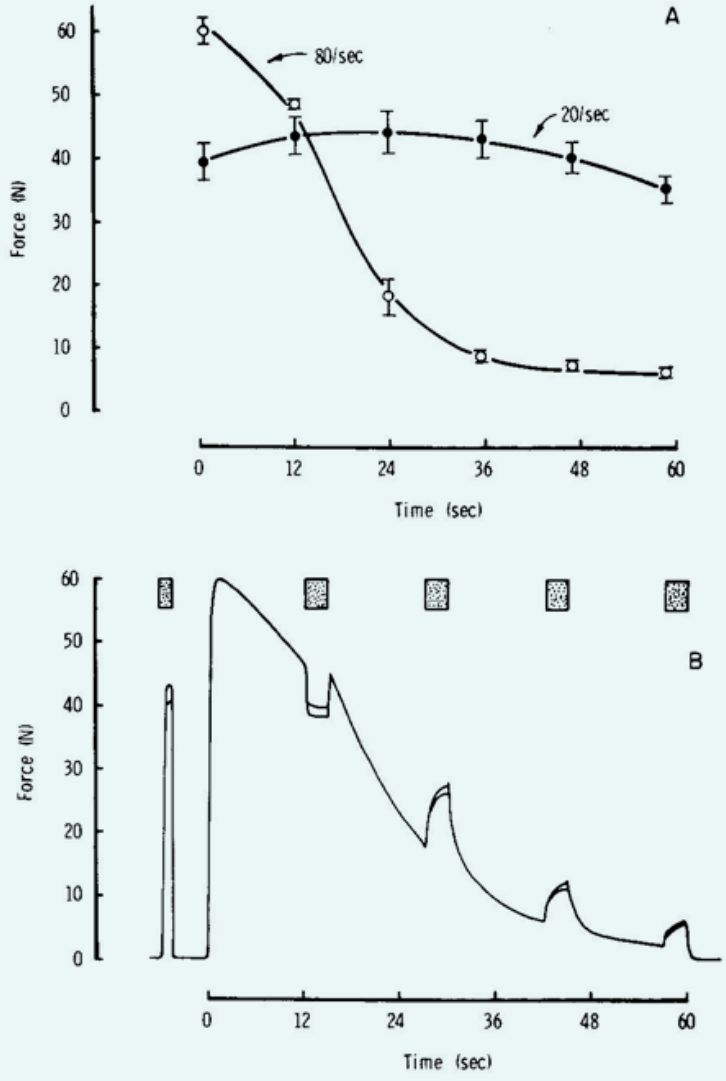

Figure 1. Force generated by stimulating the human adductor pollicis (a small muscle in the hand) via the ulna nerve with the blood supply cut off. A, stimulating continuously at either 20 or 80 Hz. B, stimulating mainly at 80 Hz but switching to 20 Hz as indicated by the stippled blocks. *Jones et al (1979)*

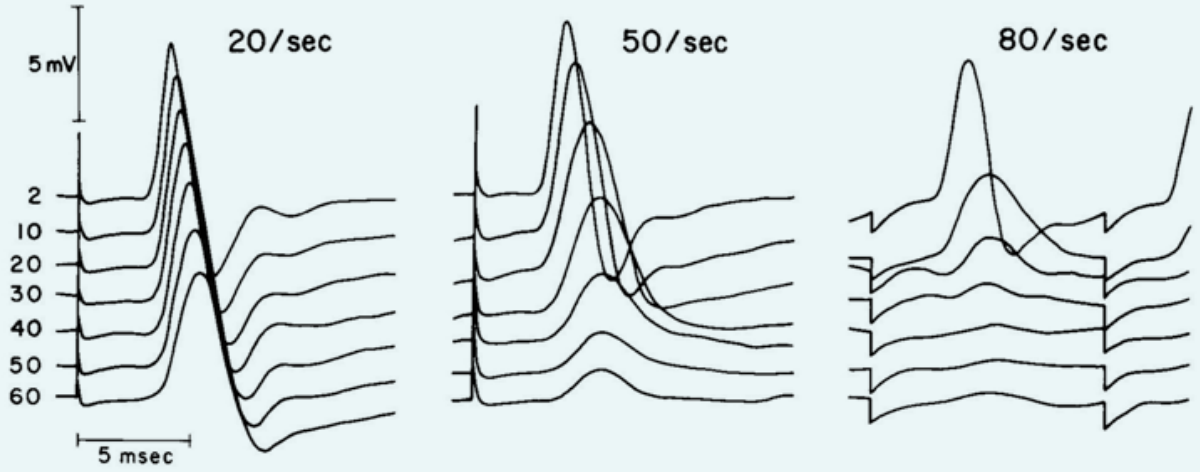

Figure 2. Action potentials recorded from the *adductor pollicis* every 10 sec during continuous stimulation at 20, 50 or 80 Hz. *Bigland-Ritchie et al (1979)*

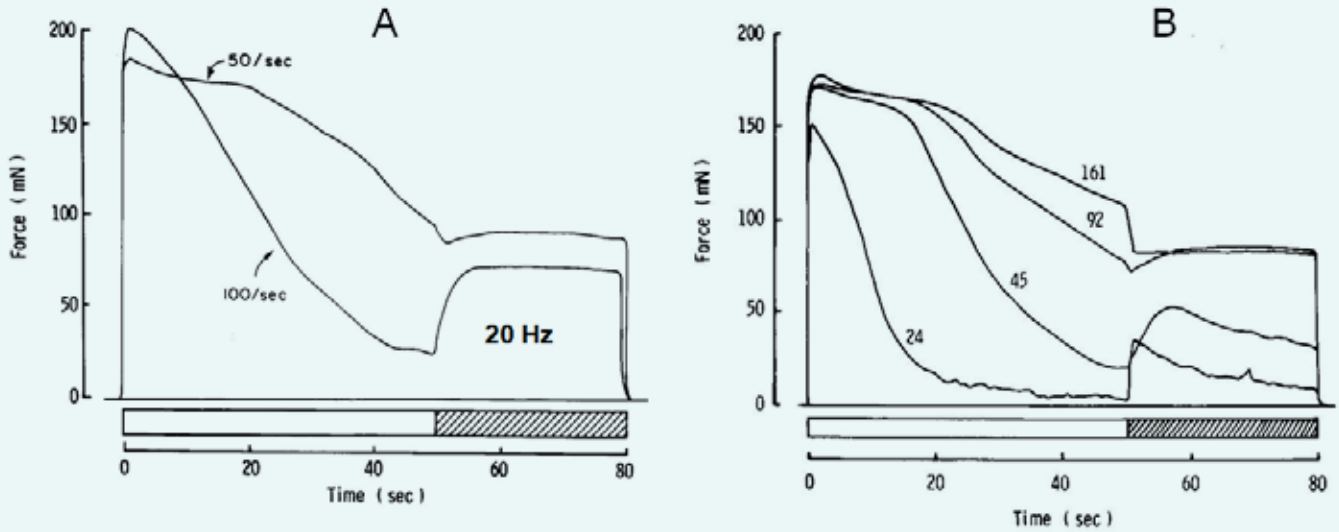

Figure 3. Effects of changing stimulation frequency with an isolated, curarised, mouse soleus preparation. A, Stimulated at 50 or 100 Hz before changing to 20 Hz. B, as in A stimulating first at 50 Hz but in different extracellular Na+ concentrations from 161 to 24 mmol. *Jones et al (1979)*

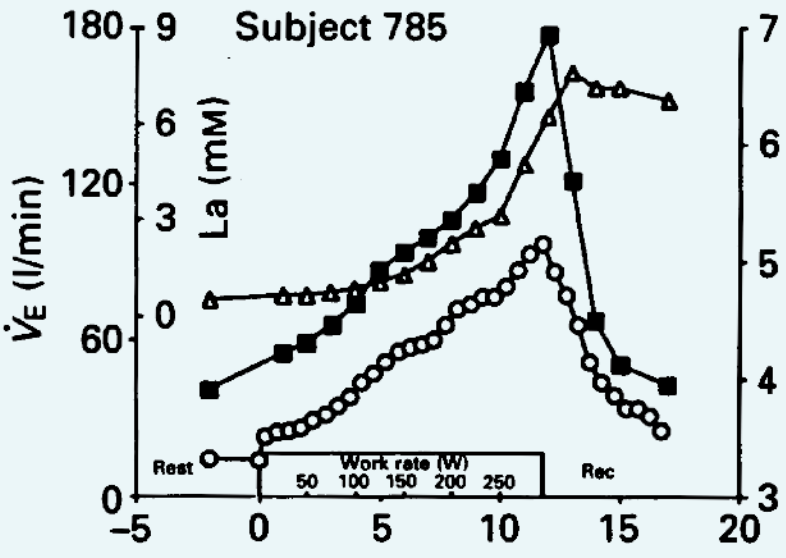

Figure 4. Changes in ventilation, blood lactate and K^+ during progressive exercise. Ventilation (V_E), open circles; Blood lactate (La), triangles; Blood K^+, solid squares. Values measured during a progressive exercise test in a normal subject. *Paterson et al (1990)*

become smaller in amplitude, as would be expected if the neuromuscular junction was failing, but also became slower with an extended wave form (Fig. 2).

Skeletal muscle fibres are tightly packed together with little extracellular space and they also have a fantastic system of T-tubules which penetrate from the surface to the interior of the fibres. The surface area to volume ratio of these tubules is huge, so that movement of cations across the membrane can very rapidly change the extracellular concentrations. Our first thought was that since the action potential is due to opening of Na^+ channels and an inward movement of sodium, then high frequency stimulation would deplete extracellular Na^+ and thus the action potential would fail. The test of this was to artificially reduce the extracellular sodium, in which case we would expect the muscle to fatigue more rapidly; and, indeed, this is what happened (Fig. 3). So I was very pleased with my first bit of muscle research and even more pleased when after a struggle with the referees, who were supporters of the neuromuscular junction theory, the paper was published.

My excitement, however, was short lived, because it was obvious that the external sodium concentration had to be reduced a long way, down to a quarter of the normal level, before any substantial change in the rate of fatigue was observed. There was also the realisation that accumulation of potassium in the extracellular space could have a much more dramatic effect on muscle excitability. There had been a report from Paul Hník of considerable increases of extracellular K^+ in working muscle, so, rather belatedly, we tried increasing the external K^+ and found it to be very effective in reducing the excitability of muscle, not only reducing force but also producing a slowing of the action potential in a similar way to that seen with intact human muscle when stimulated at high frequency.

So now I had found out that a high external K^+ is bad news for skeletal muscle and, in a similar way, I could see that it might also be bad news for cardiac muscle – something that Dr Bock already knew and, incidentally, was also known to those giving lethal injections where amongst the cocktail of drugs administered, potassium is the key lethal component. It is also known by cardiac surgeons who use a high-potassium saline solution to stop the heart beating during open heart surgery. What I wasn't clear about is precisely why it is such bad news and I remember after one PhySoc meeting, where I had presented these results, it was pointed out that by raising the external potassium the resting membrane potential would come closer to the point where Na^+ channels open and it would seem logical to expect that the muscle fibre would become easier to stimulate, not harder.

The sodium channel can be thought of as having two gates. One gate is normally shut when the internal resting potential is around -70 mV, but will open when the potential rises above a certain threshold and the sudden increase in Na^+ permeability causes the interior of the fibre to become positive (the reversal potential). However, the second gate, which is normally open when the internal potential is negative, shuts as the interior of the fibre becomes positive so that the Na^+ permeability is only high for a short interval before the membrane potential returns to the resting negative value as the K^+ permeability again dominates the charge across the membrane. With the interior of the fibre again negative, the first Na^+ gate shuts and the second gate opens ready for a next action potential. This all takes a matter of milliseconds and the closing of the Na^+ channel is known as 'fast inactivation'. However, things start to go wrong if there is an accumulation of external K^+ and the resting membrane potential is raised (i.e. closer to zero) as, over a matter of several seconds, the Na^+ channels start failing to open in the normal way in response to depolarisation, and this is known as 'slow inactivation'. I had always thought the problem was due to temperamental behaviour of the second gate, but the evidence is that slow inactivation is not the fast inactivation mechanism going wrong, but is the result of as-yet poorly understood changes in the structure of the channel.

Whether or not the mechanism is fully understood, there is no doubt that high extracellular K^+ is bad news for skeletal and cardiac muscle but the question is, how bad? Plasma potassium levels are normally tightly regulated between 3.5–5 mmol. Higher levels lead to concern and 7 mmol and above is described in the textbooks as constituting a medical emergency. Potassium is released from working muscle into the general circulation and there are many studies to choose from, but I like one in particular because it touches on a number of different aspects of the physiological role of potassium. In 1990, David Paterson and colleagues published a study concerned with the stimulus for increased breathing during exercise, in which they looked at the increase in ventilation in relation to the accumulation of potassium and lactate in the blood. It can be seen from Figure 5 that the K^+ levels reach just about 7 mmol. David Paterson is the current Editor-in-Chief of *The Journal of Physiology* responsible for, amongst other things, the highest ethical standards of published work. Now, the subject in Figure 4 was clearly reaching dangerously high blood potassium levels and so I looked carefully through the paper to see how many subjects had died or what elaborate precautions had been taken to resuscitate them as they collapsed following a medical emergency, but I searched in vain. So does this paper fall below the normal high standards expected in *The Journal*?

"The test of whether or not lactate is involved would be to study McArdle's patients, but this would be both painful and dangerous"

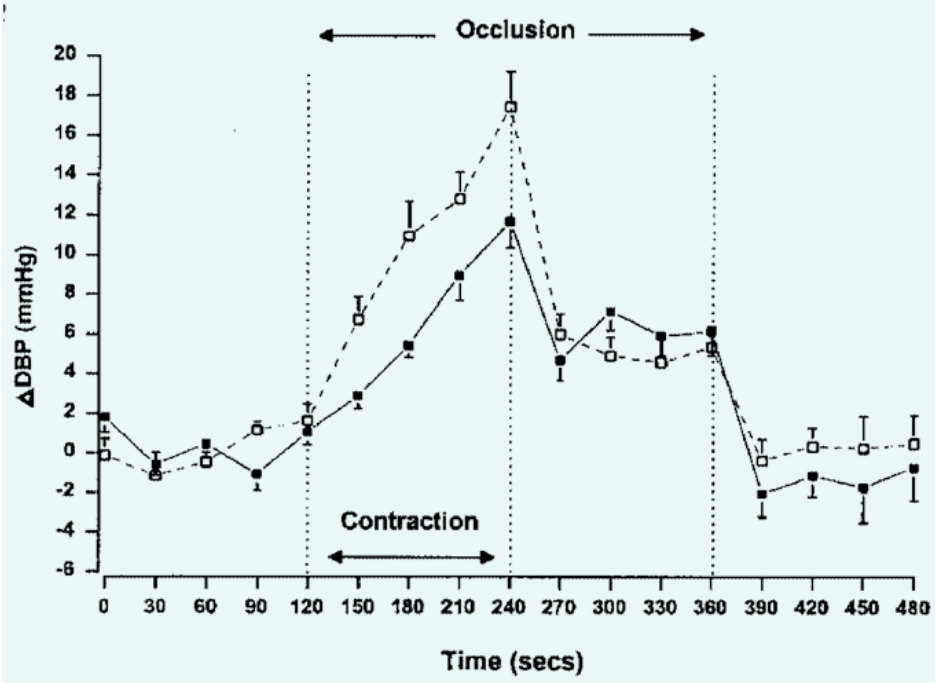

Figure 5. Blood pressure changes during a contraction and post-contraction occlusion. Changes in diastolic blood pressure (DBP) during an isometric contraction of the calf muscle and the subsequent period of occlusion. Solid line is after training. *Fisher & White (1999)*

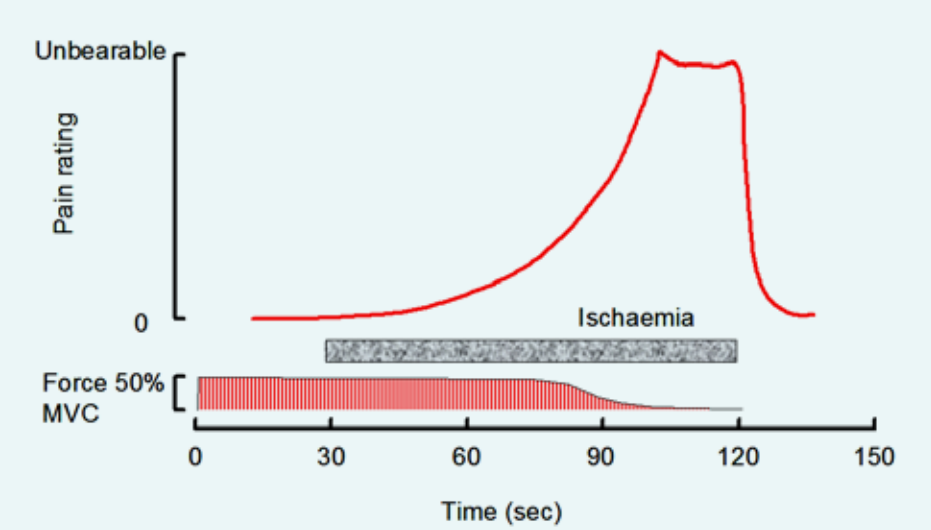

Figure 6. Schematic diagram of the development of pain in working muscle under ischaemic conditions and the continuing pain during the post-contraction occlusion phase, similar to Fig 5.

Probably not – whilst these days there is increasing nervousness about doing almost anything with human subjects, in fact we all know that this type of exercise in healthy subjects is perfectly safe. But, given the fact that, as is widely reported in the literature, blood K^+ levels can rise to 7 mmol or higher, it is not immediately clear why it should be safe.

Although 7 mmol K^+ is a medical emergency for a subject lying in bed, the same K^+ level is of little consequence with a subject exercising hard. The reason for this paradox lies in the action of the Na^+/K^+ transport ATPase which is stimulated by catecholamines released into the blood during exercise and by Na^+ entering the active muscle fibres. The action of the transporter is two-fold. First, pumping K^+ back into the cell minimises the accumulation of K^+, and may be particularly important in the T-tubules where their small volume means that K^+ concentrations can build up very rapidly. The second effect arises because the pump is asymmetric in that three Na^+ are transported out of the cell for every two K^+ coming in, exporting one more positive charge than enters the cell, acting as an electrogenic pump making the interior more negative than it would otherwise be. This counteracts the effect of potassium accumulating outside the fibre and thus the process of slow inactivation and is particularly important for the heart where raised catecholamines protect against the effects of high circulating K^+ during exercise.

The Paterson paper clearly makes the point that K^+, rather than acidosis as indicated by the increasing blood lactate, is the driving force for increased ventilation. The key point is in the recovery phase when the K^+ concentration falls rapidly, but the lactate levels remain high for at least five minutes after the end of exercise and long after ventilation has returned to baseline. The paper also contains the results of exercise in McArdle's patients who have the rare metabolic problem of not being able to breakdown glycogen in their working muscles, so they do not produce any lactate or become acidotic during exercise. The observation was that, as with the normal subjects, ventilation in the McArdle's patients increased in parallel with the increased blood K^+, but this was in the complete absence of any lactate.

Potassium clearly has an important role to play by being at least one of the factors stimulating the drive to breathe harder during exercise. To get the oxygenated blood to where it is needed it is necessary to increase blood pressure and for the arterioles in the working muscles to vasodilate. There are a number of substances responsible for this vasodilation, but K^+ released from the working muscles is an important component. Metabolites released from working muscles also influence blood pressure as has been demonstrated in some elegant experiments where a subject makes an isometric contraction with blood flow to the limb occluded with a pneumatic cuff. Blood pressure goes up during the contraction, but

when the subject stops contracting the pressure falls to about half the peak value and stays there until the blood is allowed back when it rapidly returns to baseline (Fig. 5). The inference is that about half the rise in blood pressure during exercise is due to accumulating metabolites in the muscle, sometimes known as a 'metaboreflex'.

There are a number of metabolites that could be responsible for this reflex, including both K^+ and lactate, but the speed with which the blood pressure returns to baseline when the blood supply is restored, and the analogy with the Paterson study, suggest that K^+ has a major role to play. The test of whether or not lactate is involved would be to study McArdle's patients in this way, but the evidence is conflicting, with some reporting normal pressor responses, while others say it is reduced in these patients. It would, in any case, be both painful and dangerous, since these patients experience considerable pain and their muscles tend to go into contractures if they attempt prolonged contractions.

The mention of pain brings me to the final point about the role of potassium in muscle physiology. A very common form of muscle pain develops when running up a flight of stairs, lifting weights, riding a bicycle uphill or carrying heavy shopping. It has a very characteristic feel, often described as a burning sensation, and it is a warning that the muscles are coming to the limits of endurance. It is an easy form of pain to investigate experimentally and it was first studied by Sir Thomas Lewis, a cardiologist primarily interested in the pain of angina and claudication, who in the 1930s showed that the onset and extent of the pain varied with the frequency and strength of the contractions, so that pain is essentially proportional to the work done. Furthermore, if the muscle is held ischaemic the pain persists at much the same level after the contractions has stopped and does not go away until the blood returns. The pain disappears rapidly within 10–20 seconds and the feeling is very much of the pain being washed away as the blood returns (Fig. 6). Lewis concluded that the pain was due to the accumulation of some metabolite within the working muscles and the obvious question is whether the metabolite is K^+ or lactate? Here the analogy with the Paterson study is very telling, partly because of the time course of events in the recovery period. The very rapid resolution of the pain is strikingly similar to the time course with which circulating K^+ is cleared and very different to the slow clearance of lactate. But there is another parallel; if lactate is the cause of ischaemic pain then we would expect McArdle's patients not to be affected, since they produce no lactate in their working muscles. In reality, severe pain during strong muscle contractions is a characteristic feature of these patients and, while it is impossible to tell if one person's pain is the same as another, the patients describe the sensation in exactly the same way as everybody else.

So we see that an increase in extracellular potassium plays a number of roles. It can be potentially life threatening, reducing the excitability of skeletal and cardiac muscle, and it is responsible for the ischaemic pain signaling that the muscles are reaching the limit of performance. But it also helps by increasing ventilation, raising blood pressure and causing vasodilation all of which deliver oxygenated blood to the muscles that need it most. In fact, the release of K^+ from working muscle may be seen as one of the ways of coordinating the responses of respiratory, cardiovascular and neuromuscular systems during exercise.

Chance and random events have a surprisingly large part to play in determining the direction of research just as they do for our careers and life in general. In my case, one such event took place in 1972 in a cinema at Clapham Common as I sat there wondering how it was that KCl was going to kill Dr Bock. It has taken a long time for me to realise the full implications of what potassium can do.

"Potassium is the major intracellular cation, it is found in nice things like fruit juices and, surely, drinking too much fruit juice isn't going to kill you?"

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Is the desensitization of postsynaptic receptor channels relevant?

Are ion channels more than just an open and closed case?

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Receptor-channels involved in rapid communication between neurons have historically been thought of as simple 'nano-machines' that transition between closed and open states during normal neurotransmission. However, channels can also visit a third, refractory conformation, known as the 'desensitized' state. By quantifying receptor responses to synaptic-like stimulation, we have gained better insight into how the desensitized conformation may impact receptor responses in synapses, a result that may have implications for synaptic design.

Our brains have many trillions of chemical synapses (Pakkenberg *et al.* 2003). During fast synaptic transmission, presynaptic terminals emit a series of brief neurotransmitter pulses that are sensed by neurotransmitter-gated ion channels (NGICs) located in the postsynaptic cell membrane. NGICs have both an extracellular neurotransmitter-binding domain and a transmembrane pore that can alternately adopt ion-conductive ('open') and non-conductive ('closed' and 'desensitized') conformations. The binding of neurotransmitter favors the open conformation of the pore over the closed, and thus allows ions to pass through the channel and change the electrical potential across the membrane. The magnitude of this change in membrane voltage can decrease with each successive puff, or 'pulse,' of neurotransmitter despite constant stimulation of the presynaptic neuron, a phenomenon termed 'short-term synaptic depression' (Fig. 1). This depression can affect signal transmission because, for an action potential to be propagated to the next cell, the change in the postsynaptic membrane potential needs to surpass a threshold. Indeed, if the postsynaptic response declines enough during the course of a series, or 'train,' of neurotransmitter pulses, this threshold will not be overcome, and the propagation of the signal will be prevented. Short-term synaptic depression has been observed in synapses in the brain, but there is still uncertainty surrounding the causes. In fact, several distinct mechanisms have been proposed to underlie this phenomenon, including, for example, depletion of presynaptic neurotransmitter reserves and changes in neurotransmitter release dynamics over the course of the pulse train.

In our work, we have examined one such mechanism, namely, the progressive loss of receptor responsiveness over the course of a series of neurotransmitter pulses resulting from the receptors entering the 'desensitized' state. Like the closed conformation of the channel, the desensitized conformation is non-conductive. Unlike the closed conformation, however, the desensitized state of neurotransmitter-bound receptors is very stable, and thus, desensitized channels do not open readily. The physiological role of this refractory conformation has been a long-standing mystery in the field of ion-channel research. Out of the three superfamilies of NGICs – excitatory glutamate receptors, Cys-loop receptors and

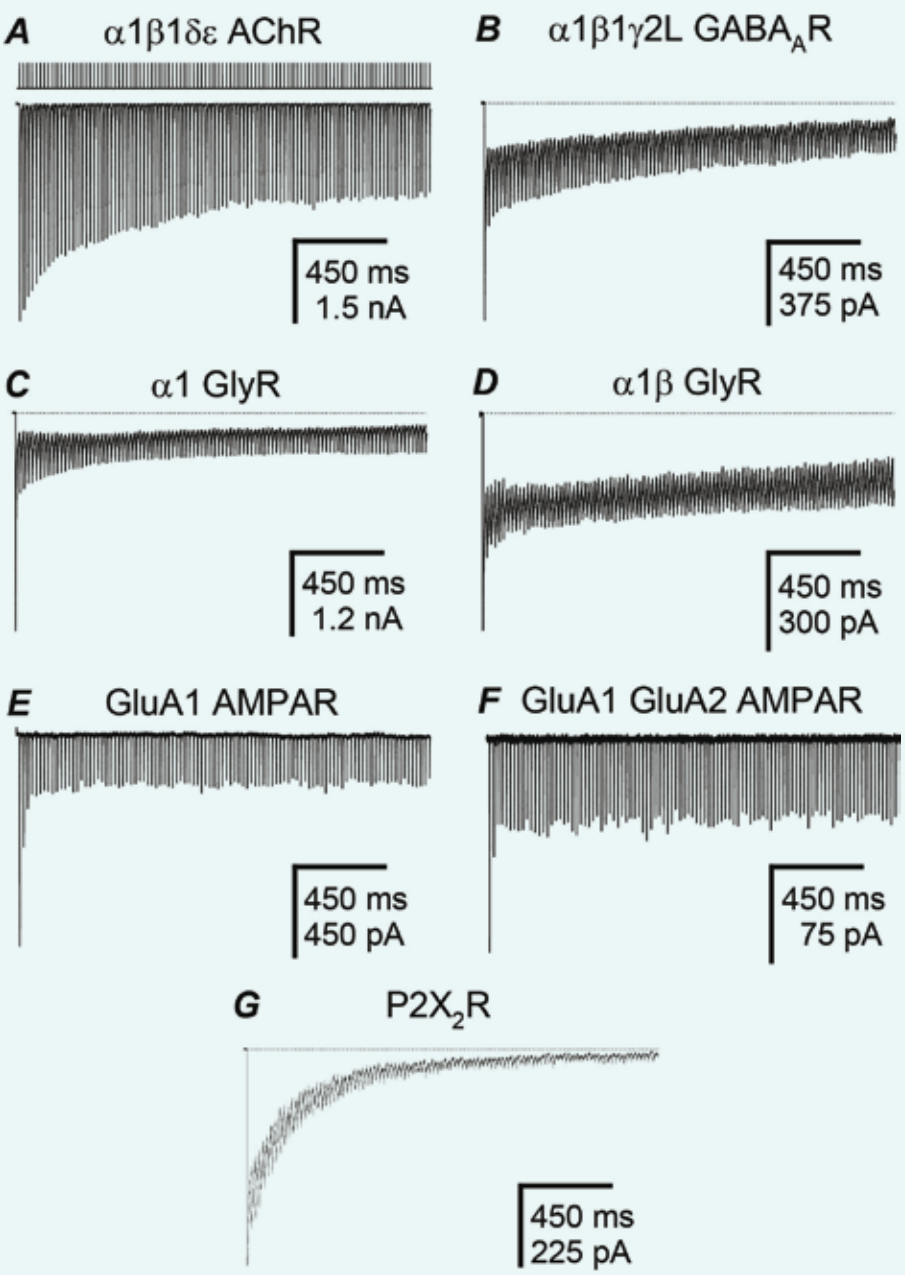

Figure 1. **Peak-current depression upon repetitive stimulation.** *A–G*, Current traces recorded from individual outside-out patches. Each panel is the response of a different NGIC to the application of a 50 Hz train of 1 ms pulses of saturating neurotransmitter for 2 s. One such train is indicated in *A* above the current trace. The zero-current level is indicated with a dotted line. The concentration of neurotransmitter was 1 mM ACh, 10 mM GABA, 10 mM Gly, 10 mM Glu and 0.85 mM ATP for the AChR, the GABA$_A$R, the GlyRs, the AMPARs and the P2X$_2$R, respectively. Although the responses recorded from individual patches exhibited high patch-to-patch variability, the traces shown are representative of the average behavior of each receptor.

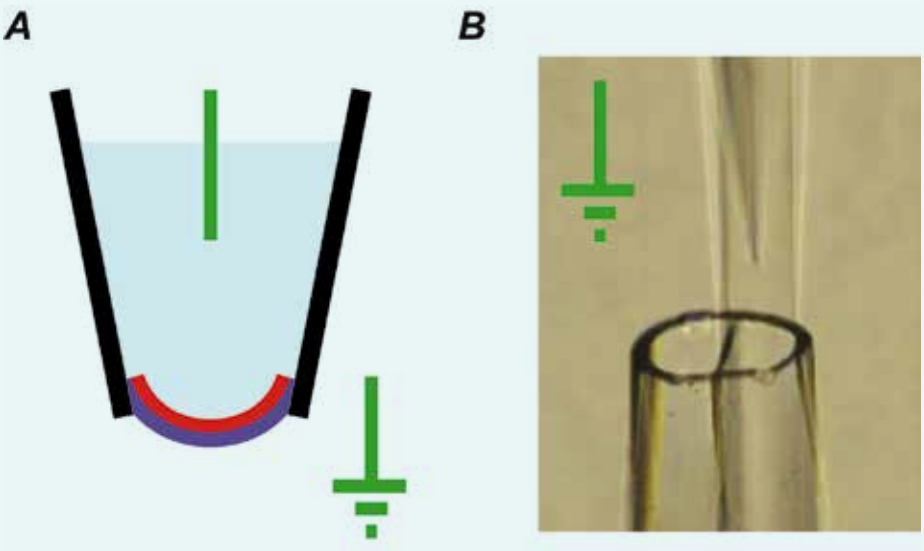

Figure 2. **Outside-out patches and our experimental apparatus.** *A*, Diagram of an outside-out patch. The outside-out patch of membrane is oriented such that the intracellular side of the membrane (red) faces the pipette solution, and the extracellular side of the membrane (purple) faces the external bath. The neurotransmitter binding domains of NGICs are oriented toward the external bath. Electrodes (green) are positioned on either side of the membrane, to enable the recording of currents passing through open channels in the membrane. *B*, Photograph of our experimental setup in which a patch pipette (top) containing an outside-out patch of membrane is positioned opposite a large, double-barreled pipette (the 'θ-tube', bottom). Two different solutions flow through the barrels of the θ-tube (one from each barrel), one with, and the other one without, neuro-transmitter. By moving the θ-tube sideways, we can apply pulses of neurotransmitter to the patch of membrane.

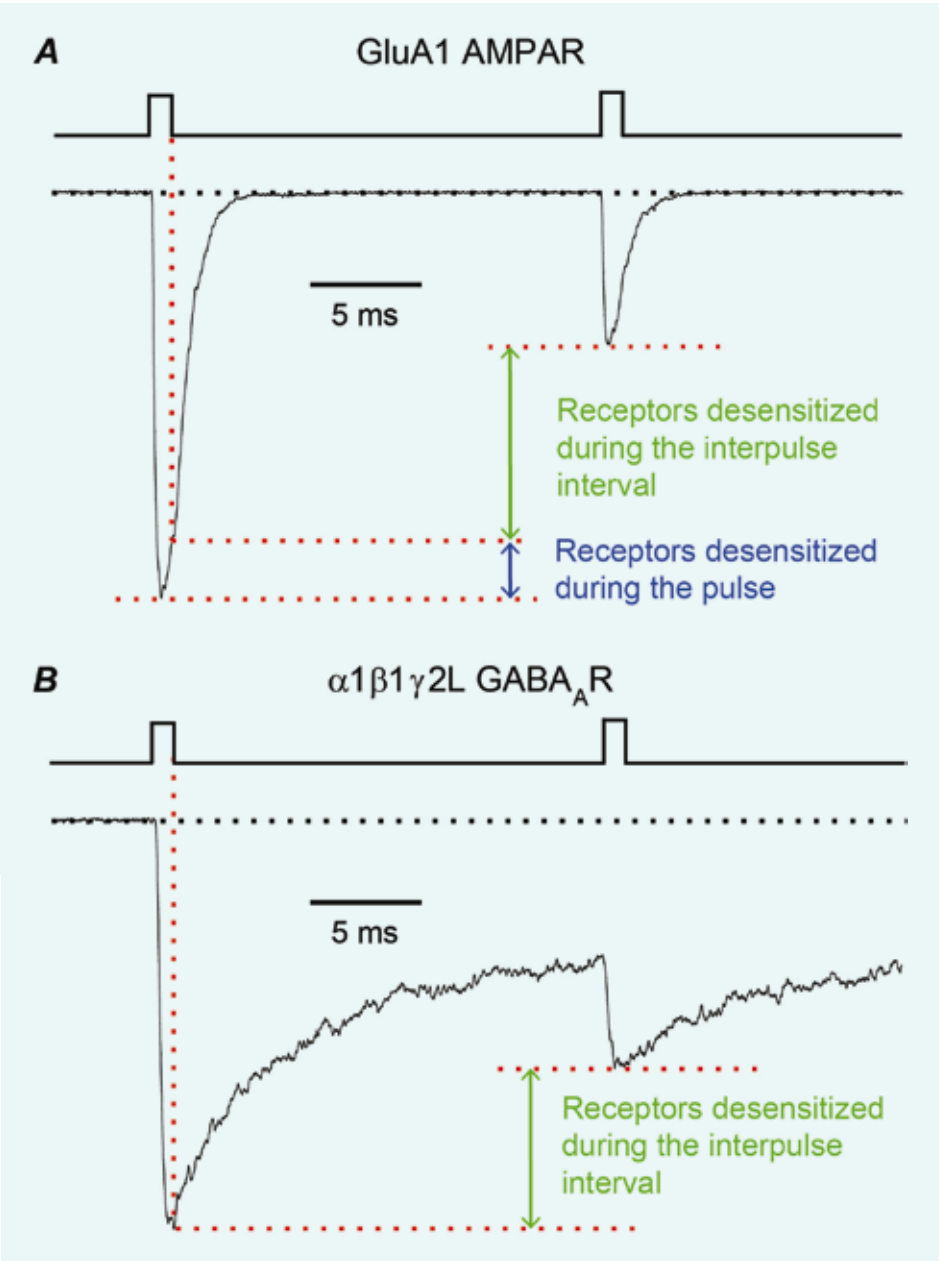

Figure 3. **Desensitization occurs mostly during the interpulse intervals.** *A*, Response of an outside-out patch containing GluA1 AMPARs to the application of a 50 Hz train of 1 ms pulses of 10 mM Glu magnified so as to show only the first two current transients. The zero-current level is indicated with a black dotted line. The red dotted lines help distinguish the extent to which desensitization occurs during the 1 ms application of Glu (blue arrow) from that occurring in between applications (green arrow), assuming negligible desensitization during the rising phase of the response. Because desensitized receptors can recover during the interpulse intervals, the extent of desensitization is actually larger than that indicated by the green arrow. *B*, Response of an outside-out patch containing $\alpha1\beta1\gamma2L$ $GABA_A$Rs to the application of a 50 Hz train of 1 ms pulses of 10 mM GABA. As in *A*, only the first two current transients are shown. Note that the extent of desensitization during the 1 ms pulse of GABA is negligible.

"It is possible that receptor desensitization allows synapses to act as low-pass filters"

purinergic receptors, altogether comprising several dozens of channels – every known channel can desensitize upon binding neurotransmitter. Indeed, applying a sufficiently long pulse of neurotransmitter to a group of receptors will force essentially all of them into the desensitized state. However, in the body, neurotransmitter pulses are generally too short (the average duration is thought to be in the 100 μs to 1 ms range) for a large fraction of the channels to desensitize during the pulse. So, in spite of its conservation among NGICs, the desensitized state has historically been deemed physiologically irrelevant (with the AMPA-type glutamate receptors [AMPARs] being, perhaps, the best-studied exception; Trussell and Fischbach, 1989). Hence, researchers studying synaptic depression have focused on other mechanisms of controlling signal transmission in synapses, while giving desensitization relatively little consideration.

Work from a number of laboratories has shown that desensitization can affect the response of AMPARs and muscle acetylcholine receptors (AChRs) to synaptic-like stimulation in excised pieces of membrane (known as 'outside-out patches' – see Fig. 2). In the case of the fast-desensitizing AMPARs, some desensitization is expected to occur during brief glutamate pulses. However, it has been shown that desensitization during the pulses cannot account for the amount of depression that is seen in response to repetitive stimulation (Raman and Trussell, 1995). Recently, it has been shown that desensitization of AMPARs is critically important for brain function – a mutation that impairs desensitization is lethal in mice (Christie *et al.* 2010). These results beg further investigation into the role of desensitization in synaptic responses mediated by these fast-desensitizing channels.

But what about slower-desensitizing receptors? As it turns out, significant peak response depression occurs when outside-out patches containing AChRs are subjected to repetitive stimulation. By examining the

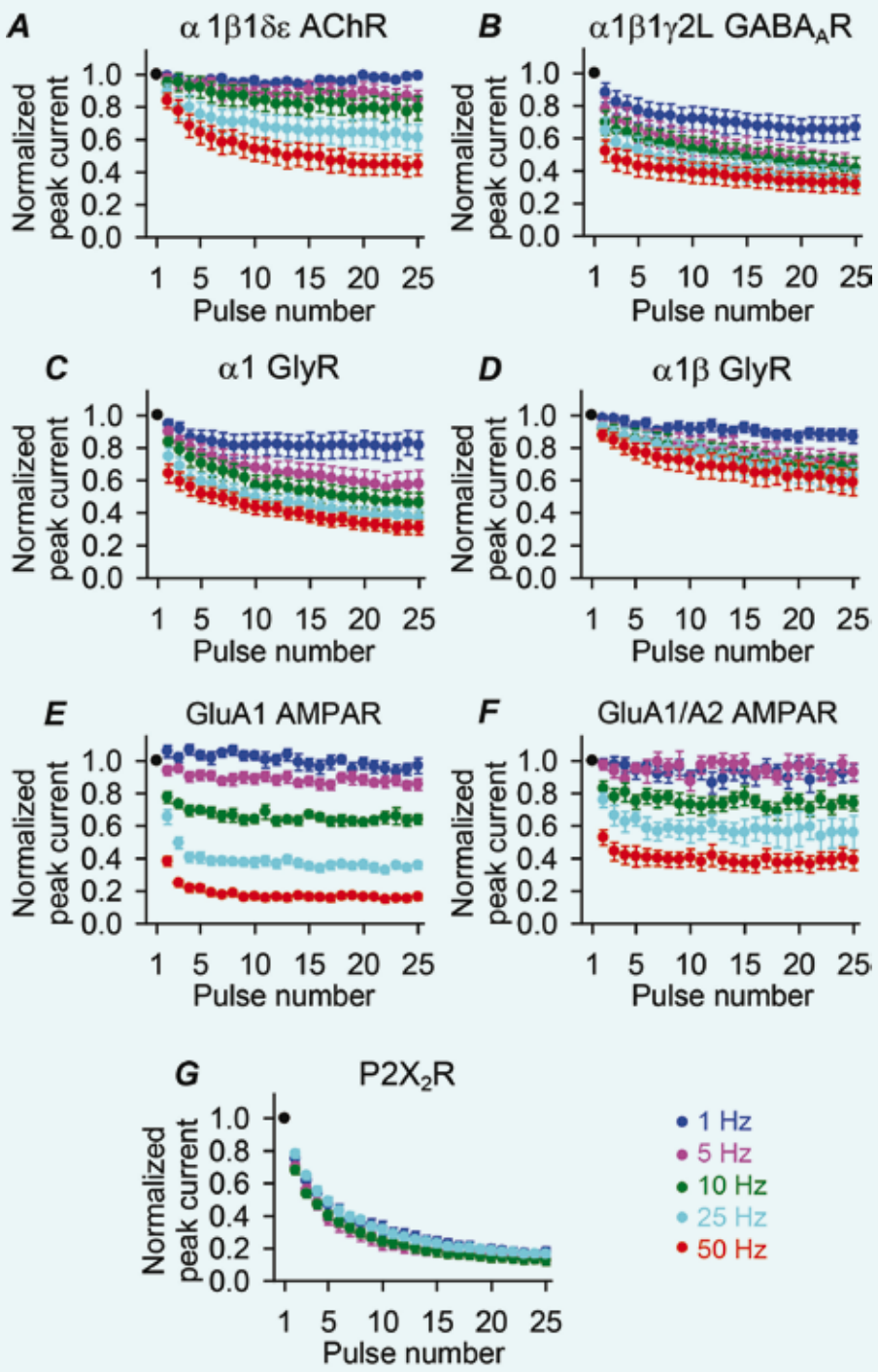

Figure 4. **Frequency dependence of depression.** Normalized peak responses to trains of neurotransmitter pulses delivered at different physiologically-relevant frequencies. Error bars are standard errors. The point corresponding to the first pulse in each train (black symbol) is the same for all trains. The colour code is: 1 Hz, blue; 5 Hz, purple; 10 Hz, green; 25 Hz, cyan; and 50 Hz, red. The concentration of each neurotransmitter was as indicated for Fig. 1.

"A synapse may succeed in repeatedly surpassing the postsynaptic threshold potential, even at high frequencies, because each individual receptor would be activated at only a fraction of the frequency of the incoming train of action potentials"

effect of both lab-generated and naturally-occurring mutations, Elenes and coworkers (2006, 2009) reported that AChRs desensitize during repetitive stimulation despite the short (1 millisecond) duration of each individual pulse. In this work, it was found that mutant AChRs with prolonged deactivation time courses (that is, with longer 'bursts' of single-channel openings, on average) exhibit more peak-response depression over the course of a train of pulses than do wild-type receptors. This finding is consistent with the idea that receptors can desensitize during the neurotransmitter-free interpulse intervals, while neurotransmitter dissociates from the receptor's binding sites. Of course, during this time, NGICs are 'unaware' of the loss of external neurotransmitter as long as their binding sites remain occupied, and so they still can desensitize. Therefore, the ability of receptors to desensitize during physiological stimulation is not limited by the duration of neurotransmitter pulses (Fig. 3).

In our recent work (Papke *et al.* 2011), we investigated whether the conclusions from work with AMPARs and AChRs can be generalized to all NGICs. To this end, we examined all types of receptors known to be

"The physiological role of this refractory conformation has been a long-standing mystery in the field of ion-channel research"

involved in fast neurotransmission – $P2X_2$ receptors from the purinergic receptor superfamily, AMPARs from the excitatory glutamate receptor superfamily, and glycine, $GABA_A$, and ACh receptors from the Cys-loop superfamily – using fast-perfused outside-out patches of membrane (Fig. 2B). Upon exposing these receptors to series of brief pulses at 50 Hz (a high, but physiologically relevant frequency), we observed a decline in the peak responses in every case (Fig. 1). Clearly, desensitization can affect the responses of all NGICs, not just the fast-desensitizing ones.

In order to put these results into a broader context, we need to consider another kinetic property of these receptors: recovery from desensitization. Desensitized, ligand-bound NGICs can 'recover' from this refractory state by returning to the closed, unliganded conformation. But recovery typically takes quite a long time, roughly on the order of hundreds of milliseconds. As the frequency of stimulation decreases, receptors have increasingly more time to recover between pulses, and as a result, there is less depression in the peak responses to stimulation (Fig. 4). Depending on the threshold for signal propagation, it is conceivable that receptors could prevent high-frequency signal transmission while allowing low frequency signals to pass through; for example, in Figure 4E, if the threshold were at half the maximal peak amplitude, then a 10 Hz signal would be propagated while a 25 Hz signal would not. Therefore, it is possible that receptor desensitization allows synapses to act as low-pass filters. Low-pass filtering behavior has been described in some synapses (Fortune and Rose, 2001), although the extent to which receptor desensitization contributes to this phenomenon remains to be determined.

Our results may superficially seem to contradict the finding that high frequency signals can pass through some synapses apparently unhindered by desensitization. However, these synapses could be structurally adapted to circumvent the limitations imposed by receptor desensitization through, for example, the use of multiple release sites with low release probabilities (note that such a system would be defined as multiple synapses by some researchers; Stevens, 2003). By having many such low-probability release sites, a synapse may succeed in repeatedly surpassing the postsynaptic threshold potential, even at high frequencies, because each individual receptor would be activated at only a fraction of the frequency of the incoming train of action potentials. Alternatively, a sufficiently low threshold for signal propagation might permit signals to pass despite a strong decline in NGIC responsiveness.

What we now know, through our work and the work of others, is that NGICs desensitize in response to brief pulses, and that, if a given set of such receptors were exposed to repetitive stimulation at physiological frequencies, then desensitization would lead to the progressive decrease of peak-current amplitudes. Along with the better-known presynaptic mechanisms, receptor desensitization could conceivably provide yet another variable for the synaptic control of signal propagation.

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Q&A: Physiological Reports

With open-access journal *Physiological Reports* set to launch this summer, *Physiology News* speaks to Editor-in-Chief, Sue Wray, and Deputy Editor-in-Chief, Tom Kleyman.

What is *Physiological Reports*? How is it different from other journals published by The Physiological Society and the American Physiological Society (APS)?

Sue Wray: *Physiological Reports* is a joint initiative between The Physiological Society and the American Physiological Society (APS). It will cover the whole of physiology, not just muscle, or neuroscience, or cellular – it's physiology in all its glory! A new open access journal will be of benefit, I would say, to the whole physiological community.

In my opinion, as a jobbing physiologist, there is a gap in the market. I currently have a couple of papers in PLOS ONE. What you get with PLOS ONE is a rapid turnaround, and as long as the work is scientifically and ethically sound, of a good standard and adds value to the literature, it can be accepted. There isn't the equivalent of PLOS ONE that serves our community, and again as a physiologist, I'd really prefer something that had 'physiology' or 'physiological' somewhere in its title to show that this work that I've submitted has been seen by experts in my field. The expertise we will get through the affiliation with the two societies will add an extra soundness and an extra degree of satisfaction that I'm published in something that bears their marks.

Tom Kleyman: We're looking for manuscripts that cover all areas of physiology, including manuscripts that are translational in nature. The story they tell may not be as complete as those papers published in one of the other APS or PhySoc journals. We're looking for solid science, but it may be an opportunity for authors to publish negative findings, which we think should be an important part of the literature, and also an opportunity for authors to publish findings that are primarily confirmatory of an important finding.

What is your background and how has it led to your leading this new journal?

Sue: I'm a professor of physiology at the University of Liverpool. I'm a smooth muscle physiologist. I guess my favourite smooth muscle is in the uterus, the myometrium, but I'm also interested in vascular and ureteric smooth muscle. I'm interested all the way from single cell studies – calcium handling by the sarcoplasmic reticulum for example – through to work on whole tissue – measuring contractility, for example – going through all the way to studies of human tissue and looking at human populations, especially with respect to child birth and labour outcomes. I think in modern parlance that makes me a translational physiologist, but for me that's what physiology has always been about; how the body works.

I've served on the editorial board of *The Journal of Physiology* and indeed I was Secretary to the Board. (I was the last person in that position – I hope that's not a bad omen!) Then, until the end of 2012, I served on the editorial board of *Experimental Physiology*. I was also on the editorial board of *News in Physiological Sciences*, the APS publication that went on to mutate into *The Physiologist*. So I have experience of acting as an editor for journals produced by both societies.

Tom: I am a Professor of Medicine at the University of Pittsburgh. I'm a physiologist as well as a nephrologist. I work on ion channels that are found in epithelial cells, primarily epithelial sodium channels, with a focus on structure-function studies.

I served for six years as an associate editor of the *American Journal of Physiology: Renal Physiology*, and I'm currently completing a six-year term as Editor-in-Chief of that journal. I have also served on the editorial boards of the *Journal of Biological Chemistry* and *Journal of Clinical Investigation*. I was on the APS committee that considered whether we should pursue an online, open-access journal and became very interested in participating in the project.

Is the trend towards open access a positive one?

Sue: I do think it's a positive, yes, and that's why, as I say, I've forked out money to publish in PLOS ONE. I think what's distinctive about *Physiological Reports* is that we're going to be gold standard open access for our societies. As I'm sure our Members are well aware, you can pay other PhySoc or APS journals to have your work published open access. However, not all authors choose to do so and thus there is a delay before content is available to all. Whereas in *Physiological Reports* everything will be accessible to everybody throughout the world from the moment it's published. So, people will have ready access to your work and it gets the message out there quicker about your research, and so you can actually move projects along faster, which is good for the subject. Our societies are also interested in teaching, and not all teachers can afford a subscription to journals to get the content they need. Also in developing countries it's a great resource for them to be able to have complete open access to what will be cutting-edge physiological research.

It is controversial, though. I mean within our own societies, we're all very grateful for the income generated from our conventional journals. What's going to happen to that income in this fluid publishing environment? I think from that point of view both societies have been extremely smart in launching *Physiological Reports*. It allows the societies to adjust their publishing portfolios to whichever way the future of academic publishing goes. It's not that we're in open access because we've been dragged there – we're here because we want to be, because we see this as a positive.

Tom: There has been an explosion of open access journals over the past decade. Authors are clearly seeking the open access format and I think both societies felt it was important to provide this type of venue for their Members and for the physiology community.

What is your vision for *Physiological Reports* and what challenges lie ahead?

Sue: Starting with obstacles, it's getting people to know about the journal and to test it. So we've got to have clear criteria for acceptance and we've got to bring our colleagues on side. People are going to be asking, "How do we know this isn't going to fold in two years' time?", or saying, "This journal will not have an impact factor for two years". We've got to sell the vision to overcome those obstacles. I think also, because there has been a glut of other open access publications by publishers who are only interested in money, we're all fed up of emails coming through – "Oh, here's the new open access journal of blah, blah, blah, send us your papers". So I think an obstacle for us is to show how we are different. I think to have the imprimatur of both societies is hugely beneficial. It puts a clear line between us and some of the other enterprises.

We're in the process of appointing associate editors and there's been such enthusiasm from the people we've approached. They've instantly got the idea of it and want to be part of it. *Physiological Reports* will be able to really take advantage of all that is coming up in the technology of web publishing and open access. I think that's exciting for many of our Members. We are scientists and we do get a bit turned on by such things!

I also hope *Physiological Reports* will bring all the physiological community together. There are some areas of physiology that you rarely see represented in our other journals. So whether what you're doing is considered 'of the moment' or not, we will be interested in that work. We won't have page limits. We won't say "We can only accept 20 per cent".

My vision is also that this will be a service to physiologists. By getting your work out in a prompter manner, you stand a better chance of getting a grant, or to progress the work.

Tom: We need to incorporate the best aspects of journal management from both societies, and from our publisher, Wiley, who obviously has extensive experience in launching scientific journals. The staff at both societies are wonderful. They're really working hard, and working together, to make this a smooth operation.

We will work with Members of both societies to encourage submissions to the journal. Society Members are key, as they are the ones who are going to be using the journal. They are going to be submitting manuscripts, they are going to be reading the manuscripts, and they are going to be reviewing the manuscripts.

There's a very positive vibe within the societies about starting this journal. I'm starting to get feedback from people who are very interested in sending manuscripts to the journal. It's very exciting.

Published simultaneously in Physiology News *and* The Physiologist*, the magazine of The Physiological Society and the newsletter of The American Physiological Society.*

Lab profile: The Clinical Pharmacology Unit, Addenbrooke's Hospital, Cambridge

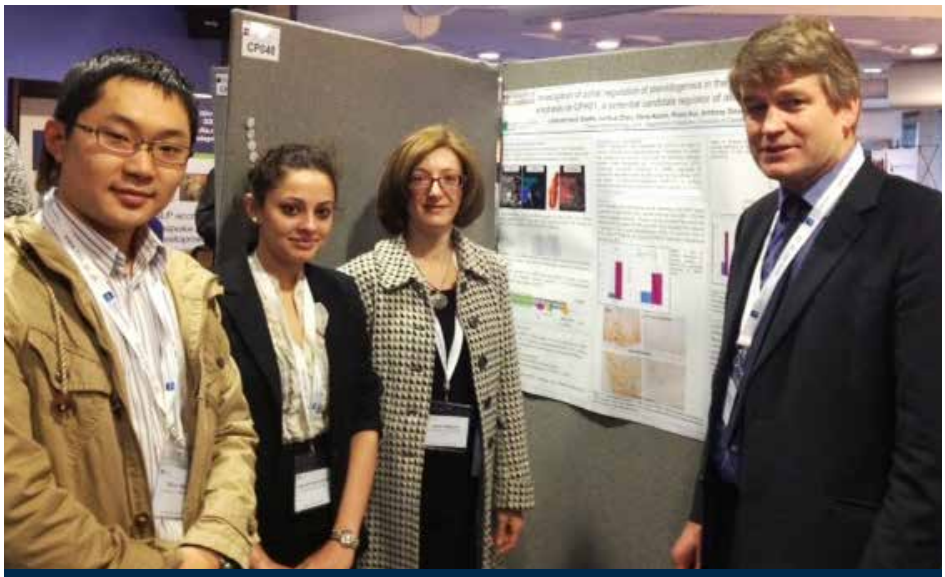
Lalarukh Haris on the laboratory in which she is completing her PhD

The Clinical Pharmacology Unit was founded in 1985 and is *the* pioneering example of the NHS funding academic developments in Cambridge. In 1998 we moved into our purpose-built clinical and basic science laboratories in the Addenbrooke's Centre for Clinical Investigation (ACCI), funded by the British Heart Foundation (BHF) and an MRC Technology Foresight grant (jointly with Cardiovascular Medicine and Neurosurgery). Although our work is mostly academic, we have been strong protagonists of translational research since long before this became common practice. Many of our research outputs are being translated rapidly into advanced practices, mainly in hypertension. We give equal weight and importance to the clinical and non-clinical members of the unit, galvanizing the clinicians to learn basic science skills, and the scientists to contribute to patient-orientated research.

Research carried out in our group focuses on hypertension, arterial stiffness, genetics of sodium handling, ischaemia/reperfusion, and cardiovascular action of G-protein coupled receptors. In addition the unit undertakes teaching of undergraduates, postgraduates and junior doctors in clinical pharmacology and therapeutics.

The Clinical Pharmacology Unit has a strong record in clinical research. Clinical trials are run in the ACCI, the Clinical Investigation Ward and Vascular Research Clinics. We run large-scale clinical trials on drug therapy in hypertension and longitudinal collaborative studies investigating novel risk factors for cardiovascular disease (e.g. CHAOS, INSIGHT and ACCELERATE). We are accelerating usage of the imaging modalities PET-CT and MRI to understand and characterise conditions such as vascular inflammation, adrenal function and

Morris Brown's lab.
Left to right: JunHua Zhou, Morris Brown, Lalarukh Haris, Carmen Maniero, Elena Azizan.



At the British Pharmacological Society winter meeting 2012.
Left to right: Peiran Yang, Lalarukh Haris, Janet Maguire, Anthony Davenport.

arterial stiffness. We use a number of non-invasive techniques to investigate vascular and endothelial function.

I did my Master's degree in the Department of Translational Medicine and Therapeutics in 2010, after which I decided to continue asking my research question in the form of a PhD. The people in my groups are engaging, helpful and motivating. Very recently I was encouraged to present a poster of my research at the British Pharmacological Society (BPS) in London and I was thrilled to win the Pfizer poster prize in the Clinical Pharmacology section.

My PhD, funded by the BHF, is supervised jointly between two eminent principal investigators in the unit. Morris Brown's research is conducted in patients with Conn's syndrome and phaeochromocytoma. He is inaugurating a BHF-funded programme of three trials investigating the role of renin measurement in the routine management of hypertension. Other current research projects include evaluation of ^{11}C-metomidate scanning for lateralisation of Conn's adenomas. He was awarded the Lilly Gold Medal by the BPS (2002) and the Walter Somerville Medal by the British Cardiac Society (2006). His introduction of the AB/CD rule, and innovations in management of phaeochromocytoma and Conn's syndrome, led to the Hospital Doctors' Award in 2003. In 2008 he co-hosted the International Symposium on Phaeochromocytoma in Cambridge.

Anthony Davenport's research focuses on understanding the role of G-protein-coupled receptors (GPCRs) that are currently the targets for about half of drugs. We use *in vitro* pharmacology and *in vivo* imaging using PET, to determine how these receptors are altered with disease. Major interests include the role of the endothelin system in cerebrovascular disease and discovering the role of novel 'orphan' GPCRS, originally predicted to exist from the human genome but recently paired with their cognate transmitters (e.g. apelin, ghrelin, kisspeptins). We collaborate with the Wolfson Brain Imaging Centre to use PET to non-invasively image receptors in vivo using novel peptide and drug radioligands. Wider research interests are reflected through membership of the International Union of Basic and Clinical Pharmacology Committee on Receptor Nomenclature and Drug Classification.

My PhD joins the knowledge and techniques from both the groups. My research interest lies in investigating a novel G-protein coupled receptor and its role in regulating aldosterone and hypertension. Primary Hyperaldosteronism (PH) or Conn's syndrome is the commonest curable cause of hypertension, affecting 5 to 15% of patients with the disease. In some patients with PH, benign tumours, which are formed in the adrenal gland(s), secrete aldosterone, the hormone which stimulates re-absorption of sodium ions in the distal nephron. In work carried out by the group we found that in a microarray comparison of aldosteronomas with their paired normal adrenals where 19,594 genes were screened, a cAMP coupled biogenic amine-like receptor; GPR61 was amongst the most significantly upregulated genes. Since GPR61 activation in vitro stimulates cAMP production, the major intracellular stimulus to aldosterone production, the hypothesise for my research is that GPR61 is a regulator of aldosterone which could be a novel therapeutic target for treatment of hypertension or other conditions associated with aldosterone regulation.

Member profile: Dafydd Walters

Honorary Member, Dafydd Walters, on how chance has affected the path of his career in physiology.

Dafydd and Robert Banks at the PhySoc Edinburgh meeting, 2012.

Since 1974, I have been employed as a clinical academic; my primary post was at London University with an honorary position in a hospital in order to practice clinical medicine, in my case paediatrics. I have just retired and what strikes me, in retrospect, is how chance has affected my career.

I studied medicine at University College London (UCL) in the late 1960s. Initially I found physiology difficult but I warmed to its ability to explain biological functions in a quantitative way and I was persuaded to undertake an intercalated degree in the subject by two people. The first was J Z Young, Professor of Anatomy whose advice in the final Second MB BS oral examination when he was obviously sorting out the sheep (the anatomists) from the goats (physiologists) was that "if you like tissues, do anatomy, if you like tissues and machines, do physiology". The second was my fellow student John Smaje (Laurence's brother) who thought it was madness to consider doing any other subject. My teachers included Andrew Huxley, Bernard Katz, David Colquhoun, Jack Diamond, Ricardo Miledi, Jim Pascoe, Otto Schild, Laurence Smaje and Doug Wilkie – but I took all this for granted (such is youthful naivety) and thought this was how physiology departments were everywhere else! But it was Alan Ness, an eccentric rather unappreciated dentist-physiologist who inhabited some intriguingly decorated rooms in the attic of the physiology department at UCL, who altered my thinking most. He taught us how to read scientific papers properly, a skill which I have found invaluable ever since.

I qualified in medicine in 1971 and did some busy junior hospital jobs and intended to train as a chest physician. However out of the blue I was offered a clinical lectureship in paediatrics by Leonard Strang at UCL in 1974. The research work in progress, when I joined him and Richard Olver, was on the development of the fetal lung and its preparation for air breathing at birth (a major paediatric clinical problem at that time, if not still, was the management of premature babies' respiratory problems). My first two years were almost totally fruitless as far as results were concerned. The main reasons were that firstly the hypothesis we were testing was wrong and secondly we were not able to realise this for some time because the results were not be available for months after performing the experiments. We did three experiments per week each producing 10 samples containing several molecular sized tracers which had to be separated by size on a sephadex gel column. Each sample produced 200 fractions and each had to be counted once if not twice for radioactivity. Counting time was 10.65 minutes per sample. You can do the sums but I can tell you that each week of samples took over six weeks just to measure before they could analysed. Nevertheless, that period was useful as I learnt many practical techniques in animal physiology and taught myself Fortran 77 (for those of you who can remember that) in order to process our data on Imperial College's main frame computer down a telex dial up line (note to the young: desktop computers did not exist then!)

The next intervention of chance came in 1977 when the professor went to France for a six month sabbatical. Within that period Richard Olver and I, fed up with no definite results, revisited an intriguing chance result from an

History and Archives Committee visit to The Society Archives at the Wellcome Trust 2006. Left to right: Bill Winlow, Saffron Whitehead, Dafydd Walters, Martin Rosenberg, David Miller, Tilli Tansey, Ann Silver.

In the lab, 2010: Dafydd, Maria Orogo-Wenn and Audra Benjamin.

Audra's PhD lunch, 2009. Left to right: Oliver Mace, Richard Boyd, Terri Tetley, Audra Benjamin, Dafydd and Debbie Baines.

experiment we had performed over a year before and had ignored because we could not understand it and assumed it was due to a technical hitch. The background to this is that the lungs of all mammalian fetuses are filled with liquid which is secreted by the lung epithelium at considerable rates (3-4 ml. $kg^{-1}.h^{-1}$) throughout gestation. In the few months of Leonard's absence we discovered that fetal adrenaline, released by the stress of labour, induced the absorption of liquid at birth. This was a novel finding which kept us in research work for a further decade, discovering the mechanism of absorption (activation of sodium channels) and the hormonal control (by thyroid hormone and cortisol) of its expression in the fetal lung at the end of gestation. It is worth noting that this finding was made well before the identification of ENaC (epithelial sodium channel). Some twenty years later, ENaC knockout mice showed its vital importance to lung adaptation at birth (Hummler et al 1996). In the late 1980s Andy Ramsden and I extended this work by examining what mechanisms existed after birth to maintain postnatal lungs relatively free of liquid and our results pointed to the appearance of a non-ENaC absorptive mechanism in adult lungs.

I was appointed to the Chair of Paediatrics at St George's Hospital Medical School in April 1994. Chance intervened again through a challenge by Sandra Guggino (Baltimore) at an ENaC meeting; asking for an explanation of what some relatively recently discovered non-selective cation channels were doing in the lung. This gave Rod Junor, a medical student just starting an intercalating PhD with me, his project: he made short shrift of it. The subsequent collaboration with Sandra Guggino demonstrated that, at least in some species, CNG1 channels (first described in the retina) appeared in the lung epithelium some months after birth. This fulfilled the prediction that Ramsden and I had made some years earlier.

In the late 1990s unexpectedly (chance once more?), I was approached to stand, I believe as the token clinician representative, for the "Committee" which then managed The Society. A few years later I became Chairman of the Executive Committee – a "doddle" they said as The Society was in future going to be run by a team of professional managers rather than the secretaries scattered around the country. Well, the reality was rather different. It was a time of enormous change for The Society. Its constitution and structure had just been altered to be fit for the new century, so that the Committee was to become the Council from which a small executive group would be elected with its own Chairman, and a President would be appointed to lead The Society and to chair the Council. Chris Fry, my predecessor, was the last Committee secretary and first chairman of the Executive; Colin Blakemore was our first President. All this coincided with a tendering for a new contract to publish The Society's journals, a move of office in London (from Dilke House to Caroline House) to accommodate increased centralisation of staff and major changes of very senior staff in the London office. It was stressful, but I was particularly grateful to the calming influence of Colin Blakemore, the practical support of Jeremy Ward (then Treasurer) and of the other Executive Committee members which at that time included Bridget Lumb, Stuart Sage, Rob Clarke, David Brown and later Gio Mann. The rocky times (and anxious ones particularly for the staff in the London and Cambridge offices) were weathered and The Society ended up with a new publisher, Blackwells, and a lucrative contract, sadly ending an association with Cambridge University Press of over 125 years. I was chairman from 2002 to 2004. It was a time of great change for The Society's way of working and apart from the structural changes mentioned above it included a reduction in the number of large meetings, the abandonment of voting on abstracts and the advent of electronic publishing. The changes were not unanimously supported!

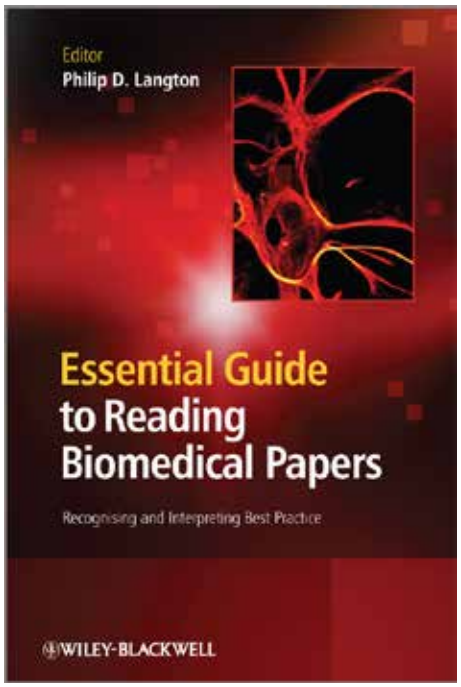
Research is not an isolated activity and I recognise the invaluable contribution of colleagues and collaborators. Chance provided me with two individuals who have been central to the research. My assistant of 22 years (Audra Benjamin) was always a totally dependable rock; she has obtained her PhD, gained a husband and borne two children and, to coincide with my retirement, has changed career to teaching. My other stalwart Research Fellow and PhD student, Richard Stephens, moved on to pastures new some years ago.

Physiology has been central to my life and I consider myself so very fortunate in the colleagues I have worked with, to have contributed to uncovering some some interesting physiological mechanisms and also had the experience of being at the centre of some major changes to The Society's working. I have been equally lucky in having had a parallel but overlapping busy and fulfilling career as a clinician. The influence of chance on my clinical career and life are separate stories!

Book review:
Essential Guide to Reading Biomedical Papers
By Philip D Langton

David Miller

Hon. Research Fellow, School of Life Science, Glasgow University



Wiley-Blackwell
ISBN-13: 978-1-1199-5996-0

It is widely acknowledged that many bio-science graduates lack significant research lab experience. Even those who have undertaken research projects can be exposed to just a few techniques. In most undergraduate courses, appraisal of research papers tends to be restricted to understanding and assessing the results or the claims authors have made; only rarely is proper attention paid to evaluating the methodology per se in order to apprehend the true significance of the work.

These widespread shortcomings extend even to postgraduate students (masters and PhD). Indeed, the reality is that few active researchers could claim a working knowledge of, or practical insights into, more than a handful of the techniques and methods covered in this collection.

These shortcomings can be greatly overcome thanks to this book. The key element is that the contributions are from active research scientists of high quality. They each address the methods in a critical sense and provide an expert's view of the advantages and pitfalls of each. There is no equivalent book currently available.

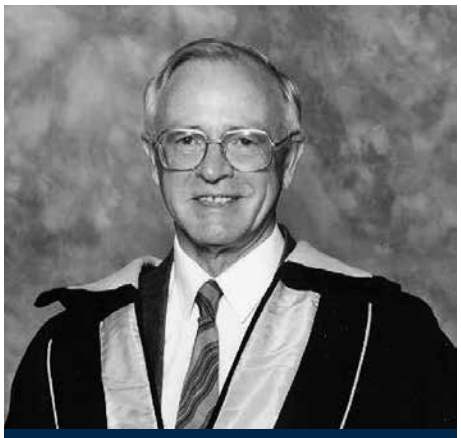
Whilst one could extend a list of 'key' methods and techniques almost indefinitely, this book provides an admirable coverage across the biosciences. The reader will acquire the right interrogative tools to bring further techniques within their grasp; what is developed here is a generic, technique-critical way of thinking as well as providing the specifics on the individual methods described.

Would you like to submit a book review to *Physiology News*?

Please get in touch with us on magazine@physoc.org

Beverly Mackenna

1929 – 2012



Beverly Mackenna

Beverly (Bev) Mackenna has died at the age of 83. The youngest of three brothers, he was born in Glasgow and educated at Jordanhill College School, a renowned Glasgow school. He excelled on many fronts beyond the academic, including gymnastics and sport, becoming School Captain and achieving captaincy of the first XV rugby team. He continued playing rugby for the school Former Pupils team at stand-off into his early thirties and was an enthusiastic golfer throughout life.

Once he had completed National Service, Bev studied medicine at Glasgow University. After graduating and completing his hospital internship, he was brought back to the Physiology Department in 1957 by the late Robert Campbell Garry whose infectious enthusiasm infused in Bev an interest in alimentary movement and the autonomic nervous system. He studied for a PhD on aspects of the latter, under the late John Gillespie, graduating in 1962. After this, he had a short post-doctoral period in the Karolinska Institute in Stockholm under Ulf von Euler, where he developed his interest in neurotransmitters. He became a Member of The Physiological Society in 1964. '*Peristalsis in the rabbit distal colon*' was Beverly's 1972 paper with his then PhD student, Hugh McKirdy (*JPhysiol* **220**, 33-54), and was much quoted. Later, when he had developed an interest in oral physiology he published original work on the masseter reflex with Kemal Turker.

For many years Beverly played an important part in the education of Glasgow medical students. Later in his career he was in charge of the physiology course for dental students. Always calm and considerate, he was well-liked and respected by students. He had a great capacity for friendship, as testified by many students of his who kept in touch with him.

Beverly was a dedicated and inspirational teacher who, in unruffled manner, could devote extra instruction to interested undergraduates and generate insight for science, dental and medical students through the years. When in charge of physiology for dental students in later years, he developed a device and mechanism for measuring jaw muscle and bite strength.

For a number of years he examined for the Royal College of Physicians & Surgeons of Glasgow and also of London and abroad; in 1990 he was made an honorary FRCP(Glasg).

Beverly's passion for brevity and precision made him ideal to assume editorial revision of later editions of the very successful *Illustrated Physiology* (Churchill Livingstone), a gem of concise and accessible basic physiological information. Originally authored by the late Ann McNaught and the late Robin Callander in 1963, and after translation into many languages, later editions were extensively revised by Bev; the sixth edition of 'Mackenna and Callander' in 1997, two years after his retiral.

Bev was a sociable and well-liked character who did not volunteer his views before consideration. Though reserved, his comments, when they did emerge, were thoughtful and incisive. He is survived by his wife Meg, his first love from school days, their daughter and grandchildren. A devoted family man, Beverly will be sorely missed by his wide range of friends, students and colleagues who knew and were influenced by him.

Hugh Elder

William Dryden

1941 – 2012

William Dryden

The Department of Pharmacology and Centre for Neuroscience at the University of Alberta, Edmonton, Canada regrets to announce the sudden and untimely passing of Bill Dryden. Bill grew up in Paisley, just west of Glasgow, and received a BSc in Pharmacy from the University of Glasgow and a PhD in Pharmacology from the University of Strathclyde. His doctoral thesis with Mary Dawson involved the development of tissue culture systems in which to examine drug effects on dissociated cells. Bill's early studies of the development of acetylcholine sensitivity in skeletal muscle ignited his interest in neuromuscular physiology and developmental neurobiology, which led him to postdoctoral studies with Sol Erulkar at the University of Pennsylvania.

Bill returned to Strathclyde as a lecturer in 1971. There he continued his work with skeletal muscle in culture paying particular attention to studies of the actions of various types of bungarotoxin. In related work, he published some of the first electrophysiological recordings from dissociated central neurons in culture. He moved to Canada in 1976 where he was appointed to the faculty in the Department of Pharmacology at the University of Alberta and where he remained until his retirement in 2008. Bill's interest in neuromuscular physiology continued to dominate his research, and this led to a sabbatical with Ricardo Miledi in London in 1982. His interest in tissue culture led to our extensive collaborations where we explored regulation of excitability of adult autonomic neurons by growth factors. More recently, we worked to develop defined medium organotypic cultures of rat spinal cord; a technique which now dominates my own research. Bill also collaborated with the late Susan Dunn in studies of multiple ACh binding sites and their relationship to subconductances in the nicotinic acetylcholine receptor. Sadly, this important work may now never be published. He was acting chair of the department between 1991 and 1992 and served as Director of the Centre for Neuroscience between 1995 and 1999. He was a well-regarded teacher and mentor to graduate students, postdoctoral fellows and faculty (including myself).

Bill spent his retirement years in the small, picturesque town of Sooke on the west coast of Vancouver Island. Here he was able to pursue his many hobbies including gardening, bagpipes and model trains. He was a true renaissance man who had an encyclopedia-like knowledge of many branches of science, literature, world history, language and architecture. Several of my colleagues remarked "he was the smartest man I ever met", we also joked that "he could probably recite the whole works of Bobbie Burns ~ in Latin". Bill Dryden was the soul of our department and we are planning to officially name our teaching laboratories in his honour. His memorial service was attended by childhood friends from Scotland as well as faculty members from Strathclyde. Several of us commented, "If Bill was your friend, he was your best friend". His insight, breadth of knowledge, collegiality and sense of humour will be fondly remembered. He is survived by his wife Angela, three children Colin, Gillian and Anna and grandchild, Jackson.

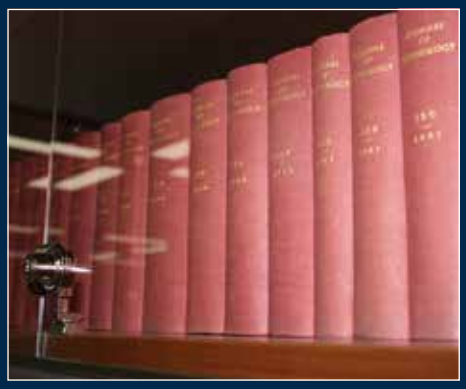
Peter Smith

The Society also regrets to announce the death of:

John Warburton Thompson

John had been a Member of The Society since 1958 when at the Royal College of surgeons in England. Since his retirement from the NHS in 1990, John continued to work in the field of chronic pain. He will be greatly missed by his family, friends and colleagues.

Journal updates



Our new library: Can you help with missing journal volumes?

The Physiological Society has recently moved the archives of the journals from Cambridge to the auditorium of the new London offices, Hodgkin Huxley House. In the process we have identified a number of missing volumes and issues. They are as follows: J Physiol 438, 446, 452, 459, 467, 473, 497.2, 578.1; Exp Physiol: 87.2. If anyone is about to dispose of an old collection, we would be grateful for these particular items. Please contact the Production Manager, Jonathan Goodchild, on jgoodchild@physoc.org

The Publications Team in their new home at Hodgkin Huxley House – all but Sally Howells who was away promoting JP at the Annual Meeting of the Biophysical Society in Philadelphia.

Introducing our new Editorial Assistant, Alexandria Lipka

Alexa says, "I've come from a life sciences research background and am very excited to be starting a new chapter in my career with the Publications Team at The Physiological Society. I'm really looking forward to my role as Editorial Administrator and am ready to take on plenty of new challenges as I learn more about the scientific and journal publishing process."

Experimental Physiology

New Editors for *Experimental Physiology* 2013

Maria Gomez
Associate Professor of Physiology at the Department of Clinical Sciences, Malmö, Sweden

Vice-coordinator of Lund University Diabetes Centre, Sweden

Research focus: vascular excitation-transcription coupling and mechanisms leading to macro- and microvascular complications of diabetes, with the aim to discover new targetable signaling pathways and develop new medicinal products.

Paul Fadel
Associate Professor, Department of Medical Pharmacology and Physiology, University of Missouri, USA.

Research focus: vascular responses to sympathetic nerve activity in health and disease under resting and exercising conditions.

Marc Poulin
Professor of Physiology, Faculties of Medicine and Kinesiology, and member of the Hotchkiss Brain Institute at the University of Calgary

Research focus: i) healthy brain aging and dementia (focusing on the impact of exercise on cerebral blood flow and cognitive function), and ii) the effects of intermittent hypoxia in health (using experimental human models) and in the pathogenesis of obstructive sleep apnea.

Karin Przyklenk
Director of the Cardiovascular Research Institute (CVRI) and Professor of Physiology and Emergency Medicine at Wayne State University School of Medicine, Detroit, USA.

Research focus: cardiac (patho)physiology, specifically the identification of cellular mechanisms and signaling pathways that increase the tolerance of the myocardium to ischemia, the development of novel strategies to limit damage caused to the heart by ischemia-reperfusion, and the translation of these concepts to the clinical setting.

Helen Raybould
Professor of Physiology at the School of Veterinary Medicine, University of California, USA.

Research focus: chemical sensing and primary afferent innervation of the gastrointestinal tract. Initially focusing on the role of gut hormones in reflex regulation of GI function but more recently extendeding to understand the role autonomic innervation of the gut in regulation of body weight and glucose homeostasis.

Out of thin air: Surviving high altitude

Join The Physiological Society on 6 April at the National Museum of Scotland to explore the unique challenges that high altitude presents to the human body and mind. Altitude sickness can range from mild confusion and nausea to death. Mountaineer Geordie Stewart will describe what it feels like to be in the 'death zone', 8000m above sea level where oxygen levels are too low to support human life.

Alongside him will be anaesthetist Kenneth Baillie, psychologist Dominika Dykiert and cell physiologist Mark Evans. They will explore how the mind, the body and individual cells are affected by high altitude. They will describe how some communities have adapted to living at altitude and explain how studying the short- and long-term effects can teach us about how our bodies function. The event will be chaired by award-winning adventure cameraman Keith Partridge.

The event is part of the Edinburgh International Science Festival and will start at 5.30pm. Tickets cost £8 (£6 concessions) and are available at www.sciencefestival.co.uk.

New neighbours

The Physiological Society are pleased to welcome Understanding Animal Research (UAR) to the top floor of Hodgkin Huxley House (HHH). UAR aims to achieve broad understanding and acceptance of the humane use of animals in biomedical research in the UK, to advance science and medicine. They engage with the public, media, policy makers, schools and the scientific research community to bring about their vision.

Wendy Jarrett, CEO of UAR, says, "We moved in to the fourth floor of HHH in mid-January and are very happy with our new space. It will be even better when the lift works are finished, although we may need to think about renewing the gym memberships we had all cancelled!"

HHH will also soon become home to The Science Council, a membership organisation that brings together learned societies and professional bodies across science and its applications. The Physiological Society looks forward to being joined by The Science Council, completing our full house.

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