PN Physiology News

Issue 93 / Winter 2013

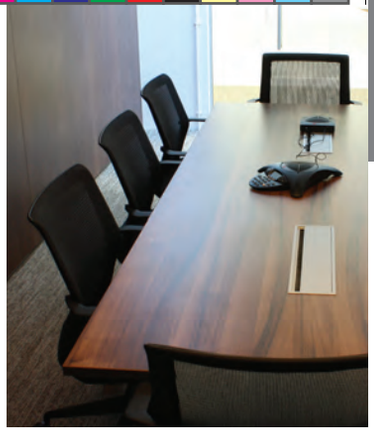
The ascent of Everest: how did physiology feature?

Why does Impact Factor still have impact?

Physical activity for physiologists

Technology update: optogenetics

The Physiological Society



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Cover image: Tom Bourdillon on the South Summit of Everest

Credit: © Royal Geographical Society (with IBG)

Exhibitors at The Society's meeting:
Epithelia and Smooth Muscle Interactions in Health and Disease
11–13 December 2013, Convention Centre Dublin, Ireland

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
Editor

The cover of this eclectic issue of *Physiology News* features a picture of Tom Bourdillon, on the Everest expedition of 1953. Without the application of physiological principles (particularly relating to oxygen, dietary and fluid requirements) to the rigours of high altitude climbing, the mountain would not have been conquered. Physiology has an obvious relevance to human physical performance, not only under extreme conditions but also in understanding and quantifying the effects of exercise in normal circumstances.

Two articles in this *PN* focus on exercise. Anton Wagenmakers and Matthew Cocks review the effects of exercise (both prolonged and short intense periods) on the function of endothelial cells. The multiple benefits include anti-atherosclerotic and anti-thrombotic effects, improved vasodilation and angiogenesis. Perhaps we are as healthy or unhealthy as our endothelial cells. It is certain that those suffering from the current epidemic of obesity, diabetes and metabolic syndrome have important impairments in endothelial function (those with metabolic syndrome also show disorders of sympathetic vascular control, see Limberg, Morgan and Schrage on page 36). Dylan Thompson makes the important point in the second article on exercise that we may be missing important information on the effects of exercise regimens by ignoring the normal physical activity levels of control subjects, which may vary markedly. Exercise isn't just about going to the gym!

PN tries to bring its readers updates on important techniques and in this issue we have two contributions on optogenetics. Gero Miesenböck talks to *PN* about the initial ideas that led to the development of these techniques and their future potential "inverting the direction of optical communication with the brain". A further article provides a review of the status of the technology in 2013 and points to some future developments and improvements that are required.

How we assess creativity and scientific quality is a continuing debate (see David Miller's update on the evils of Impact Factors on page 12). There is always the temptation to use simple metrics such as the number of times a particular research paper is cited over a defined time period. We all agree that this is a totally inadequate measure of scientific quality. In one's own field of research, one knows who is making a very important contribution and who are 'also rans', but how can this be quantified? Could an expert peer review system be applied assessing a scientist's performance? I doubt that even this would work as the most significant advances are nearly always not initially recognised by most of us as important. I remember a poster at a 1976 vascular meeting in Belgium where Bob Furchgott showed that arterial strips *in vitro* contracted to acetylcholine whereas rings of the same artery relaxed! Why should anyone be interested in such a perverse observation? However, it was the basis of the discovery of endothelial derived relaxant factors that are some of the hottest areas in physiology and pharmacology today and, some 22 years later, brought a Nobel Prize for Furchgott. Who could have predicted that?

Chief Executive's update

Philip Wright

2013 has been yet another busy year for The Society, with the highlights being the successful hosting of the IUPS 2013 Congress in Birmingham and the launch of *Physiological Reports*. This has also been the year in which we have been settling into Hodgkin Huxley House.

From the feedback I have received, the IUPS Congress was a tremendous success – I and senior members of The Society have received a lot of very positive feedback from attendees from around the world, both for the science and the organisation. Bridget Lumb and David Eisner did a tremendous job in leading the Local Organising Committee and the Scientific Programme Committee respectively, but credit must be given to Nick Boross-Toby and his Events team – Christine Carr, Ruth King and Sarah Bundock. Many other Society staff members helped out, but the Events team under Nick's leadership ensured the meeting was exceptionally well run.

Of course The Society did underwrite the meeting, but this was recognised by Council early on and appropriate financial plans put in place. It is also worth noting that our charitable objectives clearly indicate we are to support physiology 'in the UK and abroad' and the support provided to the IUPS Congress typifies the latter element.

As The Society inherited both the *Journal of Physiology* and *Experimental Physiology* (originally the *Quarterly Journal of Experimental Physiology*) from early distinguished members, the launch of *Physiological Reports* represents a first: namely the first time we have launched a new journal. Of course this has been done in partnership with our colleagues in the American Physiological Society, a partnership that is continuing to develop on many fronts.

Physiological Reports has, according to the indicators, got off to a good start. We quickly reached the 100 accepted manuscripts. As was widely advertised, this first 100 were processed for free, but with this promotion past, submissions have been maintained for our 'gold' open-access journal. A survey of authors has also indicated that the vast majority thought the overall process of submitting was either 'great' or 'good'. The number of people accessing the journal and downloading articles has been very high and well above expectations. All these indicators suggest the journal has made a good start and thanks must go to Sue Wray (Editor in Chief) and Thomas Kleyman (Deputy EiC).

Despite all this activity the Council and Executive Committee have also been developing a new five year forward plan to cover the period from 2014 to 2018, covering the term of our new contract with Wiley. The various Committees have been redefining their objectives, which have now been incorporated into the plan. The Council is reviewing and developing the draft plan and we expect to publish it early in 2014.

It is worth, prior to its publication, just mentioning a few key highlights:

- The Meetings Committee has evolved the structure of the style of meetings we will organise. Our Annual 'Physiology' meeting will continue as is, but we shall be holding two 'Topic Meetings' a year from September 2014, which mirror the Biomedical Basis of Elite Performance (BBEP) meeting in March 2012, bringing together fundamental science as well as practitioners. The first meeting will focus on obesity (September 2014) with further meetings likely to focus on ageing/degeneration (Spring 2015) and multi-scale imaging (Autumn 2015). In addition we shall be facilitating smaller meetings at local level and in our new premises at HHH. When held at HHH we are exploring how we can webcast these in a more interactive way to members who cannot attend.

- It has been some years since we have held a full review of governance – such a review is recommended every 5 years. Consequently Steering Group has been established by Council under the Chairmanship of Jonathan Ashmore, the President, and involving a number of non-Executive Trustees. An external specialist consultant has also been appointed who will be contributing her expertise from an independent and well experienced perspective.

- On the publications front it is clear we cannot rest on our laurels. We must continue to support David Paterson and Paul McLoughlin, Editors in Chief of *JP* and *EP* respectively, to ensure they remain strong. While the full impact of Open Access is still unclear, we also have to address increasing demands to provide access to data and we are working with Wiley to facilitate this where appropriate.

Philip Wright

- We need to sustain and grow our membership, especially to support early career physiologists as they progress and retain them in membership. Consequently we are looking at how we improve our membership administration and support for members at different stages in their career. We shall also look to evolve and enhance the role of Society Reps within institutions, providing a defined remit and more direct and flexible financial report.

Overall The Society is in a strong position, both financially and in terms of supporting our activities, but I hope these few highlights of our forward thinking indicate we are not taking things for granted. The Forward Plan for 2014-18 will, as I have already indicated, be published in early 2014. It is not intended to be a straightjacket, but rather a flexible road map and direction of travel.

The Society has announced that activities in 2014 will be focused around the theme of 'Understanding Obesity'. A unifying theme will lend greater impact to key activities, bringing together disparate Society functions and providing an opportunity to raise the profile of physiology in this topical issue.

Obesity: Cause and consequence

The UK has one of the highest rates of obesity in the developed world, with the majority of the population being overweight. The physiological consequences of the disease are life-threatening and cost the NHS more than £5billion each year; tackling obesity is not only important at a personal level but also on a broader economic scale.

The Society recognises the physiological causes and consequences of obesity. As many of you, our Members, undertake basic and clinical research to address both aspects of this epidemic, we want to ensure that the message spreads: whilst individuals can and should take steps to control their weight, physiologists are also working to elucidate the mechanisms that regulate body fat and to treat the diseases that obesity can lead to.

In the past decades, considerable physiological advances have been made around obesity and much on this topic has been published in our journals.

Our 'Understanding Obesity' activities

- Topic meeting
- Special issue of *Experimental Physiology*
- Focused outreach events
- And more...

We have enlisted the support of leading researchers to guide our activities and look forward to sharing details with you in the coming months. To get involved, please email our Head of Education, Outreach and Policy on **cstokes@physoc.org**

Watch our theme webpage for more action on Understanding Obesity: **www.physoc.org/obesity2014**

Save the date for our topic meeting!
The Physiology of Obesity
10–12 September 2014,
Newcastle United, UK

Outreach Grants for National Science and Engineering Week

Early spring will see National Science and Engineering Week: the annual 10-day celebration of science, engineering and technology is back again with events, activities, talks and demonstrations. The 'week', running from 14–23 March, is coordinated by The British Science Association and aims to highlight the importance of science and engineering to our lives.

The Physiological Society encourages Members to actively take part in the festivities and use the week as an opportunity to engage with the public on all aspects of physiology and promote an awareness and understanding of the subject. We are especially keen for our Members to run activities and events which link in with our theme of the year: Understanding Obesity.

Our Outreach Grants Scheme can provide up to £1000 for Members' outreach and public engagement activities. Funding can be used to cover speakers' and demonstrators' travel and accommodation, as well as resources and materials such as printed leaflets and demonstration kits. We welcome applications throughout the year with deadlines falling at the end of each month. If you hope to carry out an activity for Science and Engineering Week the deadline for applications is 31 January. For more information please see our website or contact our Outreach Officer at **outreach@physoc.org**

Physiology Feed

Bringing you snippets of the latest intriguing research

Neuronal DNA differs dramatically

The genomic structures of individual neurones differ more than expected. Researchers isolated about 100 neurones from three people posthumously and took a high-level view of the entire genome. They found that as many as 41% of neurones had at least one unique, massive copy number variation that arose spontaneously – meaning it wasn't passed down from a parent.

DOI: 10.1126/science.1243472

Lasers distinguish malfunctioning proteins

Researchers have discovered that it is possible to distinguish aggregations of the proteins believed to cause Alzheimer's, Parkinson's and Creutzfeldt-Jakob disease from well-functioning proteins by using multi-photon laser technique. If these are removed, the disease is in principle cured. The researchers now hope that photo acoustic therapy can be used to remove the malfunctioning proteins.

DOI: 10.1038/nphoton.2013.282

Kidney cells are plastic

Researchers have developed a new model for how the kidney repairs itself, adding to a growing body of evidence that mature cells are far more plastic than had previously been imagined.

DOI: 10.1073/pnas.1310653110

Light enhances brain activity

A study using three completely blind patients has shown that their brains can still detect light via a novel photoreceptor in the ganglion cell layer of the retina, different from the rods and cones we use to see. The authors believe the results raise the possibility that light is key to maintaining sustained attention.

DOI: 10.1162/jocn_a_00450

Brief steroid exposure may be permanently 'remembered' by muscles

The team investigated the effects of steroids on muscle re-acquisition in mice and discovered greater muscle mass and more myonuclei were apparent after returning to exercise after three months (15% of their life span). This cellular 'memory mechanism' may have consequences for the exclusion time of doping offenders.

DOI: 10.1113/jphysiol.2013.264457

Biology Week & Physiology Friday

After the success of last year's Biology Week, the seven-day celebration returned again for 2013. The culmination of this week-long extravaganza of activities, events, prizes and poetry, was, as last year, Physiology Friday.

Coordinated by The Society of Biology, Biology Week ran from 12–18 October and all around the UK Physiological Society Members were throwing themselves into physiology-themed activities. Matthew Manson and Jessie-Ray Matthews began the fun on the Saturday by testing the public's lung function at Cambridge Big Biology Day. Armed with a spirometer and a spreadsheet they demonstrated to visitors just how height and lung volume are related.

On Monday, The Society joined a host of learned bodies and bioscience organisations to hand out freebies at the Institute of Education for The Big Biology Giveaway. The afternoon event saw happy teachers leaving with a range of fantastic resources for their students.

Up in Leeds, Charlotte Haigh set her students into action on Wednesday in the 'Physiology Challenge'. The Leeds Students Union was taken over by human physiology Students competing against each other to carry out the best physiological outreach activity. Members of the public were treated to an investigation of peak flow rate, nerve conduction and reaction times, and a look at sleeping patterns and colour blindness. The challenge continued on Physiology Friday in a 'Cranium'-style general knowledge quiz with charades, drawing, impersonations and the spelling of some interesting physiological words – backwards. The 'Dream Team' – also known as Emma Diamond, Alex Bannister, Rhiannon James, Ellie Taylor, Melina Teske, Howard Macdonald and Tom Hall – came away victorious, nabbing themselves University of Leeds hoodies with 'Winners of the Physiological Challenge 2013' printed on the back.

A highlight of the week was Thursday night's Society-funded evening at the Royal Veterinary College. The doors of the London college opened to the public for The RVC Lates. The night featured heart-themed activities, anatomical sketching, science busking and a live dissection of a (dead) sheep, as well as a virtual reality cow simulator.

The busy week came to an end on 'Physiology Friday' with some Twitter rhymes and digestion poetry as we challenged Members and students in our Biology Week competitions. After all that fun we can hardly wait for Biology Week 2014.

Physiology rhymes

To celebrate Biology Week and Physiology Friday we ran a physiology-themed poetry competitions.

Odes to digestion

We invited under-17s to enter our digestion poetry competition for a chance to win a Kindle Fire and a visit from our Mobile Teaching Unit for their school. Entrants were asked to complete our 'Ode to Digestion' in no more than 200 words.

Apples and pears, pizzas and pies,
The food that we eat is fuel for our lives.
But there's something that happens, that stops congestion,
It's this little thing, it's called digestion...

Entries satisfied the appetite of our judges and they were impressed by the number and quality of poems received. Judging took place throughout Biology Week and Physiology Friday (18 October) and we are pleased to announce nine-year-old Rhiannon Williams of Our Lady and St Oswald's Primary, Shropshire as the winner. This is her entry:

Apples and pears, pizzas and pies,
The food that we eat is fuel for our lives.
But there's something that happens, that stops congestion,
It's this little thing, it's called digestion.

In through the mouth our yummy food goes,
Spreading energy and growth from our heads to our toes.
Teeth start chewing, taste buds awaken
And food is mushed though mastication

Our mouth glands pump out saliva and spit
To wash the food down, bit by bit
Through the gullet and into the belly,
Where all bits of food break down and go smelly.

Our stomach walls squeeze and churn
Then gastric enzymes take their turn.
Acid and bile dissolve our food
The proteins, carbs and fats we've chewed.

Round the maze of intestines the food finds its way,
Through small ones and large ones its passing each day.
As the food nears the end of the winding road,
All goodness has gone, it carries no load.

The stuff that's left must leave somehow,
Out another hole it will go now.
The waste just vanishes with a flush,
I think I've mentioned quite enough!

So if you're baffled by the question:
What on earth could be digestion?
Just take a look at this poem here,
And the answer will be written clear!

Undergraduate Prize winners

Each year, The Physiological Society awards Undergraduate Prizes to students nominated by Society Representatives. Students can be nominated for their final year project or overall performance during their degree course.

The Society would like to congratulate the following students, each of whom were awarded an Undergraduate Prize in 2013.

If you would like to nominate a student in 2014, please speak to your Society Representative.

Matthew Manning	Brunel University
Ashling Lavery	University College Cork
Monica Anne Wagner	University of St Andrews
Cáelán Taggart	University of Dundee
Joshua Davies	University of Birmingham
Gemma Scanlon	Universitry of Glasgow
Gillian Hargrave	University of Strathclyde
Rebecca Thompson	University of Manchester
Jignesh Panchal	University of Liverpool
Mrs Anzhalika Talstaya	University of Surrey
Marc Moore	Royal Holloway, University of London
Shaun Wilson	University of Wolverhampton
Madhurima Chetan	University of Cambridge
Sophie Boles	University of Bristol
Ian Duncan Anderson	Durham University
Sophie Greenhalgh	University of Warwick
Sameerah Patel	University of Huddersfield
Jack Peter Green	University of Sheffield
Joshua Akinola Fasuyi	St George's University of London
Sophie Carter	University of Essex
Friedrich Schubert	University of Aberdeen
Stephanie Solomon	University of Edinburgh
Joanna Kay Burridge	Univeristy of Leicester (joint prize winner)
Kathryn Francis	University of Leicester (joint prize winner)
Jaime Collins	Queen's University Belfast
Annie Williams	Cardiff University
Rebecca Hall	University of Newcastle-upon-Tyne
Joshua Lawley	Leeds University
Nirmitha Jayaratne	Imperial College London
James Phillips	Oxford University
Magd Alsahly	University of Hertfordshire
Lola Furlong	University College Dublin

Policy Corner

Society attends Labour party conference

From left to right – Chris Magee, UAR; Tristram Hunt, MP; Elisabeth Harley, UAR; Ed Hayes, PhySoc

The Society hosted a stand at the Labour party conference in Brighton, alongside Understanding Animal Research. During the course of the conference we met with a number of MPs, including the now Shadow Secretary of State for Education Tristram Hunt and three other members of the Shadow ministerial team.

The message from Labour on science funding was that they would seek to put in place a 10 year settlement for the science budget. However, they wouldn't commit to what level of funding would be offered or whether the funding would be inflation linked or a flat cash settlement. In the run-up to the next election and beyond, The Society will continue to push all parties for stable, increased funding.

With regards to *in vivo* research, the Labour party did not have a formal policy position in place. However, when questioned, the MPs we spoke to were of the opinion that a funded 3Rs strategy was more appropriate than the pledge the coalition government made for a reduction in overall numbers (which the government has now also realised).

House of Commons committee inquiry into women in science

The Society submitted a response to the House of Commons Science and Technology Select Committee inquiry *in vivo* into women in academic STEM careers. The submission highlighted the period between PhD completion and the first permanent academic post as a key point in which women are lost in the profession. We will be monitoring the inquiry and the resulting recommendations, and will report their findings in a future *Physiology News* edition.

Policy maker engagement

The Policy Committee will be launching a pilot policy maker engagement project in 2014, and we will be seeking members to enrol in the project, so please watch this space...

If you are interested in these or any other policy related issues please contact us via **policy@physoc.org**

Sixtieth anniversary of the famous Mount Everest ascent

Austin Elliot
University of Manchester

The Physiological Society Meeting at the National Hospital, Queen Square, on 18–19 December 1953 featured three Saturday morning demonstrations of equipment used on the famous Mount Everest ascent earlier that year, all by people associated with the expedition in different ways (see *J Physiol* vol. 123, 24P–26P). Three of the four authors – R B Bourdillon, J E Cotes and L G C E (Griff) Pugh – were career employees of the MRC and were, or became, Phys Soc Members. Two – T D (Tom) Bourdillon and Griff Pugh – had been members of the Everest expedition.

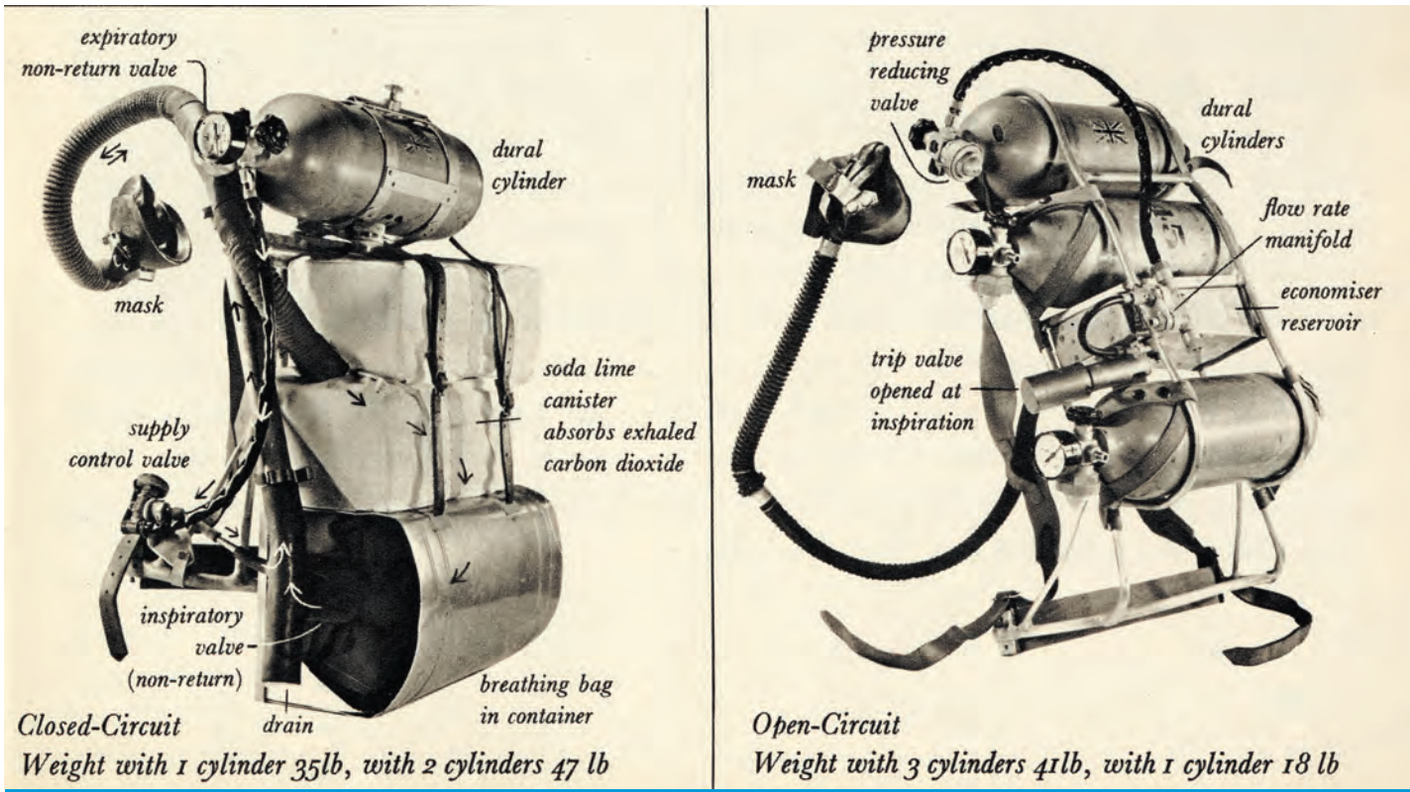
Robert (R B) Bourdillon (1889–1971) was a distinguished medical researcher, trained in medicine and physical chemistry and best-known for his work on vitamin D in the 1920s and '30s. A keen climber in his youth, from the late 1940s he directed the MRC Electro Medical Research Unit at Stoke Mandeville Hospital, which developed medical devices. His elder son Tom (T D) Bourdillon (1924–1956) was a leading climber and mountaineer of the immediate post-WW2 era, and a physicist working in rocket propulsion research. The Bourdillons were keen advocates for 'closed-circuit' oxygen sets – self-contained breathing apparatus, modelled on that devised for fire-fighting and mine rescue work.

Bourdillon senior's interest in the problems of hypoxia in high-altitude climbing was instrumental in persuading the 'Himalayan Committee' to send a physiologist on the 1952 expedition to the Himalayan mountain Cho Oyu, where the hope was that many of the logistical and physiological problems for an Everest attempt the following year could be worked out. Bourdillon suggested that Griff Pugh, who he knew of via the MRC, would be a suitable candidate due to Pugh's experience in the mountains. It was to prove a fortunate (inspired?) suggestion.

Pugh (1909–1994), then recently appointed to the National Institute for Medical Research in Hampstead, was a believer throughout his career in field research on small groups of trained or elite subjects – often with himself as subject or control, depending on the experiment. On the 1952 Cho Oyu expedition he set about systematically addressing the outstanding physiological questions, using the climbers and their sherpas as his subjects. Pugh was the first to make realistic empirically based estimates of the precise rate of O_2 delivery that would be required for strenuous climbing at high altitude. Another key insight that was to pay dividends the following year was that fluid loss (mostly via increased respiration) was a major concern. Pugh set down calorie and dietary requirements, and recognised the importance of the climbers' sleep and recovery for their ability to maintain conditioning. All his recommendations, summarised in a famous (though unpublished) report, were to prove critical for the successful 1953 Everest ascent.

Pugh continued his researches at altitude as a member of the Everest expedition, though the climbers did not always prove the most willing subjects. Following the expedition Pugh was overwhelmed with juggling post-expedition commitments – attending functions and giving large numbers of seminars through the latter part of 1953 and 1954 – and trying to pick up the threads of his earlier research on survival in cold water. As a result the appearance of his Cho Oyu and Everest data was delayed, with the papers not appearing in *J Physiol* until 1957 and 1958. They contain much of interest, including measurements on both the Everest 'summiteers' Ed Hillary and Tenzing Norgay.

The 1953 expedition took along both 'closed-circuit' and 'open-circuit' oxygen equipment. The former was widely agreed to be the ideal solution if it could be made to work reliably at altitude, though only the Bourdillons believed it could. The closed circuit system closely resembles the classic undergraduate physiology experiment of re-breathing from an O_2-filled spirometer, with exhaled CO_2 removed by absorbing it with soda-lime ('an extended period of normal breathing'). This system delivered close to 100% O_2 to the climber, and also greatly reduced respiratory fluid loss. However, the closed-circuit sets proved temperamental and unreliable in the mountains. Tom Bourdillon and Charles Evans were forced to abandon their summit attempt using them when one of the sets malfunctioned still 300 ft, and 2 hours climbing, short of the peak.



Credit: © Royal Geographical Society (with IBG)

Left, R B Bourdillon and T D Bourdillon – closed-circuit oxygen apparatus as used on Mount Everest, 1953. Right, J E Cotes – the open-circuit oxygen equipment used by the British Mount Everest Expedition.

Hillary and Tenzing, in their successful summit attempt 3 days later, used the technically simpler and more robust open-circuit oxygen equipment. This was derived from wartime RAF oxygen equipment, but had been modifed by John E Cotes, who worked at the MRC's Pneumoconiosis unit in Cardiff. The modifications reduced resistance to airflow in the apparatus – vital when a climber's lungs might be moving 100 litres a minute – and also adapted the masks to avoid the valves freezing in the sub-zero air. The rates of O_2 delivery were based on Griff Pugh's research.

Of the December 1953 authors, John Cotes, then only in his 20s, went on to a long and distinguished career in respiratory medicine and research – including authoring one of the definitive textbooks on lung function, now in its sixth edition. R B Bourdillon retired in 1955, moving to British Columbia where he took an interest in early years education. Tragically, Tom Bourdillon was killed in a climbing accident in Switzerland in 1956. Griff Pugh, finally, has got his due as a pioneer of applied physiology with a wonderful biography written by his daughter Harriet Tuckey (see review later in this issue).

Credit: © Royal Geographical Society (with IBG)

Griff Pugh samples expedition leader John Hunt's alveolar air. Pugh's 1957 paper gives Hunt's alvoelar pO_2 at Camp III, 20,500 ft (6230 m) above sea level, as 40–50 mmHg, less than half the expected sea level value.

Why does Impact Factor still have impact?

David Miller
Glasgow University, UK

Surely not another rant against the Journal Impact Factor (ImpF)? We all know ImpF is no way to represent anything much of interest or relevance about either the journals we publish in, or the publishing scientists themselves, right?

But wrong, apparently, so far as one hears and reads almost daily. The imminence of REF (the Research Excellence Framework) – the latest exercise designed to assess and define government funding of research universities in the UK – brings this thorny issue back out yet again (see e.g. Richard Naftalin's article, 2013). Beyond REF, it cannot be overlooked that ImpF has (allegedly) been deployed for many years by grant-giving bodies and by university appointment and promotion committees too. So, here we go again...

Informed rubbishing of ImpF has a long history (see e.g. Colquhoun (2003); Molinie & Bodenhausen (2010); Seglen (1997); Wouters (2013)). But despite the erudition and overwhelming technical evidence of its invalidity, league tables based on ImpF haven't been killed off, yet. An impressive plea to abandon ImpF in any academic context was made earlier this year: the San Francisco Declaration on Research Assessment (DORA, 2013). Signatories include AAAS, Wellcome Trust, EMBO, PNAS, PLOS and our Society's journals, but importantly in the context of REF, also by the UK's Higher Education Funding Councils. Despite DORA's powerful plea and its supporting case, the Research Deans in British universities have not abruptly altered their practices, allegedly.

For this article, I had hoped to be able to quote chapter-and-verse about REF submission criteria, at least for the Russell Group universities. However, for fear of institutional retribution and career suicide, nobody was willing go on the record about their own employer. Thus, all I can do is to report what others have told me 'in confidence'. It is quite clear that Research Deans – or whoever is leading the task of deciding whose papers, and which papers, are in or out of REF – are ruthlessly using ImpF in their deliberations about physiologists. However the techniques are being dressed up for public consumption, it is obvious that the laudable guidance and explicit instructions about quality assessment processes given in the REF documents (see e.g. REF, 2011) is being ignored. The practice is clearly widespread and, given the published guidelines ('No sub-panel will make any use of journal impact factors, rankings, lists or the perceived standing of publishers in assessing the quality of research outputs.' REF, 2014), surprisingly explicit, or so I am assured 'off the record' by respondents from several Russell Group institutions.

The sharp edge for physiology, of course, is that de facto, an ImpF of 5 is being seen as the lower boundary for submission of papers (in basic medical sciences where most physiologists will be returned). This arbitrary cut-off is in large part fuelled by the relatively high ImpFs 'enjoyed' by many clinical journals. (More on this detail later.) It is thus a matter of considerable professional anguish that *The Journal of Physiology*, indubitably a leading international journal in our discipline, had an ImpF of 4.380 for 2012. (Perversely, so many significant figures are reported for an 'index' lacking significance!) It is clear (e.g. from David Paterson's report to the Society's AGM in July at IUPS 2013 in Birmingham) that, although *The Journal of Physiology* editors are signatories to DORA, they still feel constrained by Realpolitik to do everything they can to 'enhance' this potentially devastating 'metric'. Even the Society's website reports the ImpF of *J Physiol* and *Exp Physiol* prominently.

ImpF, as you will be aware, only looks at the total number of citations gained by a given journal over the two calendar years immediately before the census date (explaining why I have long preferred the term 'Ephemerality Index' for ImpF). It is interesting to note that Eugene Garfield (1998) – who had himself devised ImpF in 1963 with I. H. Sher – noted the large relative enhancement of 7-year and 15-year citation indices for 'long impact' journals like *J Physiol* when compared with ranking by their 'standard' 2-year ImpF. These critical caveats – and many more – are wilfully neglected by those still in the thrall of ImpF.

The reader might need a refresher course in ImpF 'bibliometrics'. David Colquhoun (2003) succinctly provided the principal criticisms of ImpF per se:

(a) 'high-impact journals get most of their citations from a few articles'

(b) [ImpF deploys] 'the unsound statistical practice of characterizing a distribution by its mean only, with no indication of its shape or even its spread'.

In support of these points, Colquhoun exemplified for (a) that *Nature* (in 1999) achieved half its total citations from just 16% of its articles and for (b) that 69% of a random sample of 500 biomedical papers over a 5-year count period had fewer than the mean citation score (of 114) whereas one paper had been cited at more than 20 times that mean. *Nature* itself (2005) quotes similar examples from 2002–3 against, as-it-were, its own enviable ImpF.

Now let us take a closer look at examples with immediate relevance to physiology. *The Journal of Physiology* captured a total of 46,000 citations in the last ImpF 2-year window. Of these, nearly 800 were for a single paper, one published in 1952. Yes, it's Hodgkin and Huxley (vol. 117, pp. 500–544). The annual citations of this seminal work have been rising almost linearly since 1952 (Fig. 1).

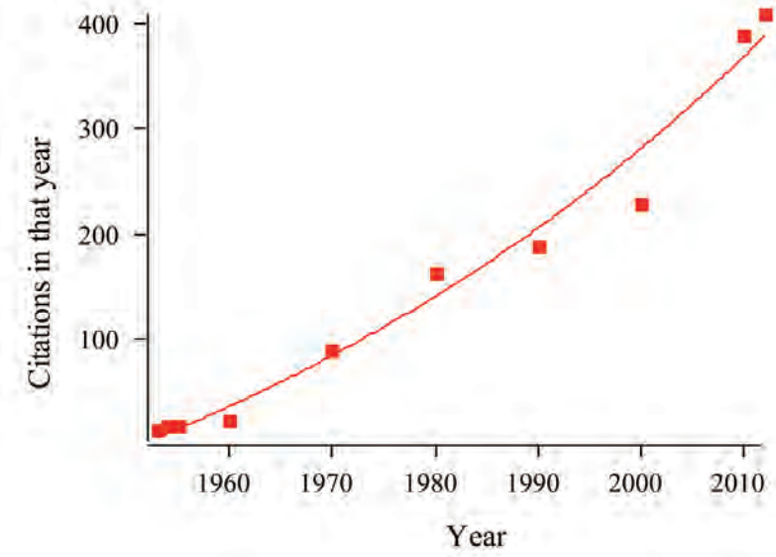


Figure 1. Citation pattern for Hodgkin & Huxley (1952)

Nothing about ImpF can capture the real impact of a paper of this kind, rare though it is, not even its citation impact. Equally, ImpF fails to capture the 'average' *J Physiol* papers either. These tend to accumulate citations over several years, generally after a 'slow' start (in ImpF terms). The half-life for *J Physiol* papers (the time taken to accumulate half their eventual total citations) is longer than 10 years. Many might argue that this is real impact.

To illustrate these points, I have taken at random one issue of *J Physiol* (vol. 553, issue 3, the last in 2003). I have compared its ImpF-relevant data with that from the last 2003 issue for *Circulation*, a physiology-relevant journal, but one that has a much higher ImpF (largely by dint of citations by its huge clinical-academic readership). For medicine-dominated REF submissions which will generally include physiologists, the comparison is salutary; in ImpF terms, *Circulation* is 'in', but *J Physiol* is 'out'. Figure 2A and B shows the raw citation data after 2 years (i.e. the numbers contributing to ImpF for 2006) and after (nearly) 10 years for both journals. The data points represent the individual citation totals (ordinate) of each of the 28 *J Physiol* papers (Fig. 2A, abscissa) and 18 *Circulation* papers (Fig. 2B) in the respective December 2003 issues. Each curve shows, as with almost every journal, that just a few papers are heavily cited, but that most are cited very much less. The general shape of the citation profiles looks broadly similar at 2 and 10 years for each journal, albeit on different scales. But to facilitate comparison, the data are then replotted with each normalised to the maximum citation numbers for 2 or 10 years (Fig. 2C and D). The shape of the normalised profiles for *Circulation* (Fig. 2D) is now seen to be little different between 2 and 10 years of accumulated citations. However, for *J Physiol*, the shapes are clearly different. After 10 years, several papers have disproportionately gained citations relative to the best-cited one. We can even calculate a 'normalised ImpF', the average citation rate of all papers expressed relative to the most-cited one. This 'normalised ImpF' after 10 years is almost unchanged from the 2-year rate for *Circulation* (0.34 vs. 0.37 of the maximum, respectively), whereas for *J Physiol* it is some 40% higher (0.35 vs. 0.25). These profiles are for just one, randomly chosen issue of each journal. They show why ImpF fails, even on its own crude terms, to provide a satisfactory 'metric' of the impact of papers in *J Physiol* whereas for *Circulation* it is at least more consistent over time. (Some highly rated journals such as *Nature, Cell* and *Neuron* and many clinical journals show falling 'impact factors' for citation periods of longer than 2 or 3 years; examples of 'brief impact', perhaps?) Finally, the histograms of the data from panels A and B are shown (Fig. 2E and F). These skewed plots further confirm why a crude average 2-year citation rate (i.e. ImpF) is inadmissible as a description of citation pattern, confirming Colquhoun's points (a) and (b) above. (For readers interested in a recent analysis of statistical, and other, anomalies inherent in ImpF, see Vanclay (2013). The author shows (his Table 5) the huge discrepancy of mean (=ImpF), median and modal citation rates for a range of journals, amongst many other damning details.)

In the numerate sciences, an attempt to deploy a 'metric' like ImpF within an article would be rejected by the referees out of hand ("Methods Section: The skewed, non-normal distribution of our statistic will be represented by its arithmetic mean."). Meanwhile, the same journals are virtually forced to agonise about their own set of Emperor's Clothes in the crazy fashion-world of ImpF. Worse, senior scientists and academic clinicians who, as referees, would decry this spurious 'metric' do use it – allegedly – in making decisions about staff hire-and-fire, research quality assessment, funding and research strategy. Bosses might publicly claim (as they must) that their assessment of publication quality is ImpFindependent, yet a cursory glance at the 'approved journals' lists at every UK Research Dean's elbow – allegedly – reveals congruence with ImpF 'data'.

Publishers could claim, with some justification, that ImpF is part of their 'real world', even though they profess to hate it. If that is true, then it is we academics who are to blame for having ever given it any credence. It really is up to the academic community to acknowledge the stark nakedness of the Emperor ImpF as any sort of a 'metric'. The 'justification' that ImpF is 'rough and ready' or 'the best we have' is grotesque. Perhaps our infatuation with ImpF is like that for Schools League Tables, the *Sunday Times* 'Best Universities' tables and all the rest; we just can't resist taking a peek.

Finally, there is growing interest in author-specific citation ratings, typified by the 'H-factor' (Hirsch, 2005; Bishop, 2013). But even this approach must be treated with great caution, as the online debate of a recent *Nature* article by Macilwain (2013) clarifies: here Paul Soloway remarked: "In the 10 years since [the] 1950 PNAS paper was published in which Barbara McClintock described the seminal work that earned her Nobel Prize [1983 for Physiology or Medicine], the paper was cited only 30 times and received a minimal amount of attention [Fedoroff, PNAS 109: 20200-3 (2012)]. I can only imagine how McClintock would have been judged if the H-factor counters been born and subjected her to their scrutiny. There is no metric for creativity."

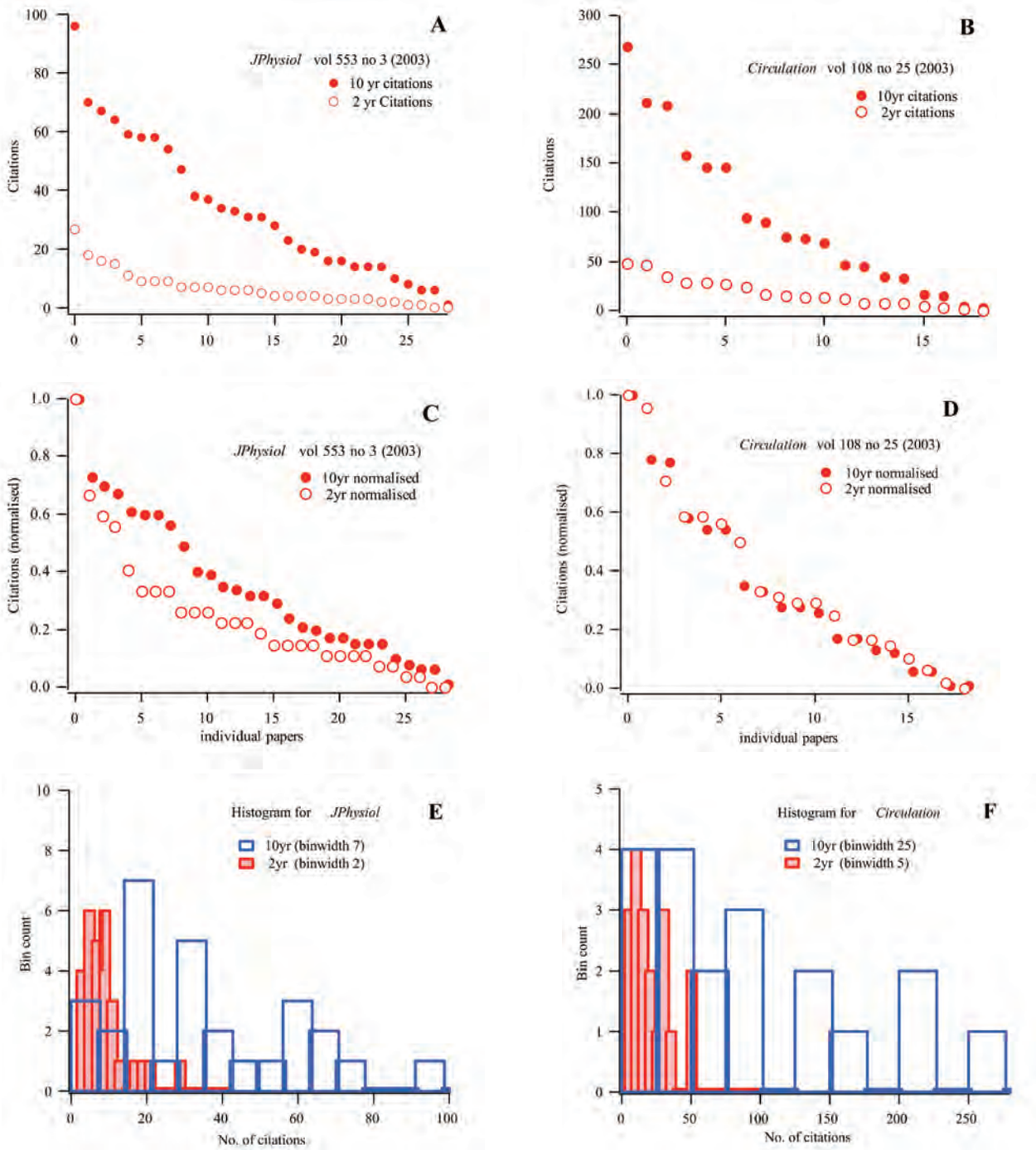


Figure 2

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Techniques Workshops 2014

An introduction to Molecular Biology

1–4 April, Birkbeck College, London, UK

This workshop is for physiologists who want to learn the basic yet essential techniques used in molecular biology. It will also illustrate the principles and methodologies behind the manipulation of protein expression using a variety of transfection techniques.

Organised by Dr Caroline Pellet-Many, University College London.

CGR Advanced Course: "Genome-Wide Expression Profiling"

7–11 April, University of Liverpool, UK

An introduction to the conceptual, practical and interpretational issues involved in large-scale gene expression profiling.

Organised by Professor Andy Cossins, University of Sheffield, and Dr Marta Milo, University of Liverpool.

Live-Cell Imaging

17–19 June, University of East Anglia, Norwich, UK

A theoretical and practical guide to imaging live cell and tissues, designed especially for beginners.

Organised by Dr Paul Thomas, University of East Anglia.

Real-time Quantitative PCR

10–11 July, King's College London, UK

Delegates will extract RNA, reverse transcribe it and measure expression of a gene by qPCR. Data analysis methods will also be covered. Practical aspects are complemented by short lectures.

Organised by Dr David Sugden, King's College London and Dr Patricia de Winter, University College London.

31st Workshop: Microelectrode Techniques for Cell Physiology

3–17 September, The Laboratory of the Marine Biological Association, Plymouth, UK

Intensive residential workshop teaching the practical application of miscroelectrode, patch clamp and optical techniques to single cells and tissues.

Organised by David Ogden, Colin Brownlee and Alexandra Street, Marine Biological Association.

www.physoc.org/techniques-workshops

The Physiological Society

2014 *Forthcoming events*

29 April

JP Symposium:
Insights gleaned from pharmaco-genetic dissection and modelling of cardio-respiratory neural networks
San Diego Convention Center, San Diego, United States

30 April

EP Symposium:
Physiological and pathophysiological signalling between the gut and the kidney: role in diabetic kidney disease
San Diego Convention Center, San Diego, United States

30 Jun – 2 Jul

Physiology 2014
The Queen Elizabeth II Conference Centre, London, United Kingdom

10–12 Sept

Obesity – A Physiological Perspective
Newcastle Upon Tyne, United Kingdom

Meeting Preview

Physiology 2014

30 June – 2 July 2014, The Queen Elizabeth II Conference Centre, London

London will play host to Physiology 2014 and we are delighted to be back at The Queen Elizabeth II Conference Centre in the heart of Westminster.

This year the meeting will start with The Presidential Symposium, hosted by the year's outgoing President, Jonathan Ashmore. This is a new feature for The Society's Main Meeting, and this year's topic of 'Emerging technologies for physiology and neuroscience' only alludes to the strength of the scientific content.

Many of the most popular sessions at IUPS 2013 were the workshops that were held at lunchtime, and as these were so popular and beneficial to career development, we are holding many of them again. Immediately after 'The Presidential Symposium' you can choose to go to sessions including:

- Statistics
- Publishing for beginners
- Women in Science
- Effective presentation skills
- Massive open online courses (MOOCs)
- Media training

Feedback from previous meetings has shown that these sessions are important for many research active physiologists, and so we are delighted to be able to hold workshops to share best practice, and to provide a forum for discussion.

Another key feature for any Society meeting is the opportunity for early career scientists to be able to share their work. Each symposium includes two early career scientists (which means within five years of obtaining their PhD). There are two poster sessions and also an afternoon of oral communications on the first day.

Oral Communications are a highlight of any Society Meeting, giving those early on in their career a platform to share their work and hone their presentation skills. This is why it has a dedicated slot in the afternoon on the first day. Each of the seven Themes will be represented and will have its own stream. Those giving an oral communication can opt to enter The Pfizer Prize. We award up to six prizes of £250 at The Society's Main Meeting.

Robert Winston will then give The Annual Public Lecture on Monday 30 June from 18:00 – 19:00. The other prize lectures to be given at this Meeting are:

- Annual Review Prize Lecture – Professor Richard Tsien (New York University, USA)
- Joan Mott – Professor Dame Linda Partridge (University College London, UK)
- Paton Lecture – Professor Peter Sleight (John Radcliffe Hospital, Oxford, UK)

No Society Meeting would be complete without the Welcome Reception and also the Society Dinner. The Welcome Reception follows Professor Winston's lecture at Central Hall of Westminster, a stone's throw away from The Queen Elizabeth II Conference Centre. Drinks and nibbles will be served, and there will be entertainment. It finishes at 20:30 leaving you plenty of time to go for dinner.

Robert Winston

For the dinner, we take advantage of the fabulous location of The Queen Elizabeth II Conference Centre, and their award-winning chefs will serve up a marvellous three-course meal, with wine and entertainment, overlooking Westminster Abbey.

We are delighted to be back in London for the Main Meeting, last hosted by UCL in 2006. It also gives you the chance to visit Hodgkin Huxley House, and see the facilities that The Society has.

For further details please visit:
www.physiology2014.org

Meeting Notes

‘DABfest’: Celebrating a remarkable contribution to ‘Ion channel regulation and neuronal physiology’

19 July 2013, Royal Society, London, UK

Sue Jones

University of Cambridge, UK

Annette Dolphin, Mala Shah & Trevor Smart

University College London, UK

It is 33 years since the published discovery of the ‘M current’ for which David A. Brown (FIBiol, FRS) and his colleague Paul R. Adams (FRS) are so well known (Brown and Adams, 1980). This voltage- and time-dependent, non-inactivating K^+ current limits subthreshold neuronal excitability; muscarinic receptor activity inhibits M current, removing the “brake” on excitability and enabling membrane depolarization. David is internationally renowned for his work on M (and other) channel biophysics, function and regulation. In addition, David has led with distinction the Pharmacology Departments at The School of Pharmacy and University College London and held visiting Professorships at the Universities of Chicago, Iowa, Texas and Kanazawa and a prestigious Fogarty Scholarship-in-Residence at the NIH.

Throughout his career at St Bartholomew’s (1967-73), The School of Pharmacy (1974-87) and UCL (1987-2002), David has trained over 20 PhD students and 30 postdoctoral researchers and has hosted 15 visiting researchers with a tireless commitment to international collaboration and scientific exchange.

In recognition of these contributions, a one day symposium on Ion channel regulation and neuronal physiology (affectionately dubbed ‘DABfest’) was held at the Royal Society in London on 19 July 2013. The symposium was organised by Mala Shah and Trevor Smart and was supported by The Physiological Society, The British Pharmacological Society and UCL. Over 100 of David’s colleagues, collaborators, friends and visitors from around the world came to hear inspiring talks, to reacquaint and to reminisce.

Thomas Jentsch (Leibniz Institute for Molecular Biology) gave the opening plenary presentation on KCNQ channels in the auditory and vestibular apparatus, highlighting their functional and clinical significance (thereby reminding us just how important the M current discovery was). In a session dedicated to the M current, Mark Shapiro (University of Texas, San Antonio) told us about ‘The Elusive Transduction Signal’ (PIP2), and Naoto Hoshi (University of California, Irvine) described the importance of co-ordinated local intracellular signalling for M current regulation. The functional role of M channels in pain sensation was described by Nikita Gamper (University of Leeds), and Mala Shah (UCLSoP) revealed the contribution of M channels to axonal excitability.

After lunch, other ion channels appeared on the menu, some of which David has worked on during his career, including Ca^{2+}-activated K^+ currents (Neil Marrion, University of Bristol), ion channels in osmosensation (Charles Bourque, McGill University Canada) and GABA-gated Cl^- channels (Trevor Smart, UCL). The focus then turned to synapses: the role of nitric oxide (John Garthwaite, UCL), an intriguing perspective on LTP (Paul Adams, SUNY at Stony Brook), and in the closing plenary presentation Roger Nicoll (University of California, San Francisco) gave a modest and very entertaining account of his experiences in the fields of synaptic ionotropic and metabotropic receptors.

DAB with gift at speakers’ and sponsors’ dinner

This one day symposium captured beautifully David’s wide interests in ion channels, and the talks were received with interest and enthusiasm from a packed room. But alongside the science was a sense of great personal warmth towards a man who has fostered an international scientific family over the past 45 years.

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Symposium attendees outside the Royal Society

Meeting Notes

Talking Physiology in India

The Physiological Society International Prize, 20 February - 10 March 2013

Richard Vaughan-Jones

University of Oxford, UK
Deputy President, The Physiological Society

Richard Vaughan-Jones receives a commemorative plaque, after his lecture, from Professor Sanjeev Mishra, Director of AIIMS, Jodhpur

The invitation by The Physiological Society to deliver its International Prize Lecture in India came as I arrived back from a previous tour of the country. I had visited in late 2011, on a travelling fellowship awarded by Exeter College, Oxford, where I am an Official Fellow. It had been my first trip to India, and I returned with my gastro-intestinal function intact, and with no other ailments. So India was not such an intimidating place after all! I had delivered research lectures in universities and Institutes in Mumbai, New Delhi and Hyderabad. But it had become clear to me that I was barely scratching the surface of scientific activity in India. So I jumped at the opportunity of returning, this time on behalf of The Physiological Society.

The International Prize Lecture is peripatetic within a given country, delivered in several scientific venues, in order to strengthen links with The Physiological Society. Jonathan Ashmore, Society President, had just attended the 100th Indian Science Congress in Kolkata, at the invitation of the local Physiological Society. So I travelled instead to the desert city of Jodhpur (west of Delhi, to a newly opened All India Institute of Medical Sciences: AIIMS) where there was a meeting of national medical school directors, engaged in the design of a new teaching curriculum. After that, it was south to the tropical warmth of Trivandrum in Kerala State (Rajiv Ghandi Centre for Biotechnology). Then back north to the crowded roads of New Delhi (to the country's first AIIMS), north again to the cooler climes of Panjab University in Chandigarh (a city developed by the architect, Le Corbusier) and, finally, east to historic Lucknow (King George's Medical University), academic home of the great Indian neurophysiologist, Paintal, and where I delivered a lecture at the brand new and impressive premises of the Central Drug Research Institute.

King George's Medical University, Lucknow. (R-L) Head of Physiology Prof. Sunita Tiwari, Mrs Elena Vaughan-Jones, Prof. Richard Vaughan-Jones, Vice Chancellor Prof. Devendra Gupta, Prof. Onkar Tripathi

When combined with my previous visit, that made ten talks in seven cities, in two years. So I have had a snapshot of the health of Indian life-sciences, and of physiology in particular. Unfortunately, one city that beckoned, but with no time to visit, was Bangalore, which houses important national neuroscience research. That must await another trip, should the opportunity ever arise.

The roving lecture, "Ca^{2+}/H^{+} exchange in the heart: a key element in health and disease", was a summary of recent cardiac research from my group and co-workers in Oxford, including Pawel Swietach, and my long-standing collaborator, Kenneth Spitzer, in Salt Lake City, USA*. The lecture was a full-on integrative cellular physiology talk, focusing on signalling, intracellular H^{+} and Ca^{2+} ion homeostasis, membrane ion transporters, and sub-cellular ionic trafficking. It was informative, therefore, for me to gauge the audience response. I was happy (and not a little relieved) that reaction was positive, appreciative and enthusiastic. A not infrequent cry in the Institutes, however, was that India does not "do physiology". Integrative cellular work, even when it addresses clinical issues, is being superseded by molecular and genetic approaches, combined with the ever present search for clinical markers of disease. Not unique to India, you might think, but a more rational balance between clinical and basic science has certainly been struck in the UK, which still permits serious physiological approaches to important medical questions. This has been complemented in general by the rise of systems biology, which is quantitative physiology by any other name. India may now need some of this, to bridge between its notable molecular and genetic research and its delivery of efficient and modern clinical care. The problem of invisible physiology, however, is not always as acute as may initially seem. Although India apparently does not "do physiology" as much as it might, it certainly does neuroscience and biophysics. It is just that these subjects do not always assume their rightful position under the umbrella of physiology. Like systems biology, they are physiology by another name. This issue is recognised by the two main Physiological Societies in India (Physiological Society of Kolkata, and the Association of Physiologists & Pharmacologists of India [APPI]). But it would benefit from being promulgated more roundly.

Curiously, physiology as a named discipline is not necessarily in decline in India. Funding of science is currently a priority there, and resources are increasingly being committed. Most impressive is a building programme of six new AIIMS centres, to complement the original in New Delhi. Each centre comprises a new medical school, a dedicated hospital of up to 1,500 beds, and an allied research institute. The new AIIMS buildings, their full clinical and research staff, and their attendant medical students are deliberately sited in the more deprived regions of the country, such as Bhubaneswar, Raipur and Patna, where local medical care has not, until now, been self-sufficient. The six new AIIMS represent a truly massive infrastructure investment by the government, which is to be applauded. When I was visiting the new AIIMS, Jodhpur, I was impressed that the recently appointed medical directors were inclining towards a traditional departmental model of medical teaching within their centres. This includes teaching (and research) based around Departments of Physiology, Anatomy, Pathology & Pharmacology. A remarkable endorsement of a structure that is rapidly disappearing from university medical schools in the West. But for new physiology to flourish as research in the new AIIMS, it must embrace not only molecular and genetic disciplines, but also cutting-edge physiological applications of optical and magnetic resonance imaging, and modern biophysical, electrophysiological and computational techniques, applied at cellular and sub-cellular, as well as organ-system and whole-body level. And this requires investment. Then physiology will provide the much needed bridge between molecular and clinical science.

An enlightened approach to the combination of teaching and research does not always prevail in India. The real money sits in the Research Institutes, which are rising like new Maharajah Palaces on the outskirts of cities, stocked with up-to-date equipment, and

manned by highly qualified and dedicated research personnel. If infrastructure funds are maintained (a crucial point), these will match anything in China, Japan or the West. In contrast, investment in medical research is notably at a lower level in many of the universities, where the culture is to emphasise teaching. Once again this dichotomy is not unique, but the contrast in India can sometimes be stark. It can be argued persuasively that excellence in teaching stems from excellence in research discovery. Divorcing one from the other is not always beneficial. For example, elite universities in the UK, like Oxford, Cambridge and London, can only survive as coherent establishments if the link between teaching and research is maintained in an interactive manner. Separation of the scientific palaces in India from higher education in the universities runs the very real risk of a less inspirational educational delivery.

Overall, my Indian experience was immensely positive. I am extremely grateful to my hosts throughout the country, in particular S Sircar & S Mishra (Jodhpur), CC Kartha (Trivandrum), R Mathur (New Delhi), A Grover & R Tewari (Chandigarh), and O Tripathi (Lucknow). Above all, a huge thank-you is owed to Subrata Tripathi (TIFR Mumbai, & Bhubaneswar; Subrata is a longstanding member of the UK Physiological Society) who helped me plan and execute both trips to India. Reflections after the tour are that the flagship Institutes for life sciences are progressive beacons and the main engines of discovery in India. But universities must also have the means to thrive. The Vice Chancellors whom I met in Chandigarh and Lucknow, for example, are actively developing both research and teaching activity in tandem in their universities. This must surely be allowed to redress some of the balance with the stand-alone Institutes. Lastly, the new AIIMS are truly outstanding ventures. I hope that the embrace of physiology as a continuing key subject in medicine is backed by investment in its power for research. This time, my return journey to the UK was not greeted with another ticket to India. But I trust it is not too long before I have the pleasure of greeting friends there again.

**Swietach P, Youm JB, Saegusa N, Leem CH, Spitzer KW, Vaughan-Jones RD (2013) Coupled Ca^{2+}/H^{+} transport by cytoplasmic buffers regulates local Ca^{2+} and H^{+} ion signaling. Proc Natl Acad Sci U S A. May 28;110(22):E2064-73.*

The old - King George's Medical University, Lucknow

The new - main entrance to AIIMS Jodhpur

Young Life Scientists' Symposium 2013

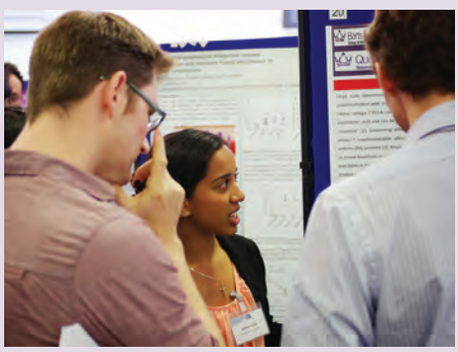
6 September 2013, Queen Mary University of London, UK

Andrew John Leese

Queen Mary University of London, UK

The Young Life Scientists' (YLS) Symposium is an annual scientific conference co-sponsored by the Biochemical Society, the British Pharmacological Society and The Physiological Society. Organised by young scientists, for young scientists, the YLS symposia provide a great opportunity for students and early career postdocs to come together, present their work, and network with other scientists in their field. Each symposium focusses on a separate scientific theme with this year's event, hosted at Queen Mary University of London, entitled: 'Cardiovascular Medicine: Bridging Basic and Clinical Researchers'. This represents a timely and significant subject as heart disease continues to represent a leading cause of morbidity and mortality across the world, highlighting the need to produce new innovative drugs and improve existing therapies. Effective translational medicine – the process in which discoveries made in the laboratory are applied directly in the clinic – is undoubtedly central to achieving this goal. This requires collaboration across multiple disciplines, which is a practice that the organising committee were keen to encourage amongst the next generation of research scientists at this year's symposium. In this light, both basic scientists and clinicians in the field of cardiovascular research were invited to give an oral or poster presentation with the emphasis of relating their work to the wider context of translational medicine and communicating in a manner that could be easily understood by a diverse research audience.

Indeed, the YLS symposium 2013 proved to be a massive success, with more than 65 of the 150 registered delegates submitting an abstract for presentation. Both the oral presentation and poster sessions were highly engaging, prompting plentiful questions and lively scientific discussions. This extended to the keynote lectures, given by Ingrid Fleming, Rhian Touyz and Mike Grocott, all of whom kindly shared their pioneering cardiovascular research and interacted superbly with the young delegates. Another highlight of the day's programme was the satellite sessions, which focussed on encouraging young scientists to pursue a career in medical research and included advice on how to write a telling CV, as well as a talk by a research advisor from the British Heart Foundation detailing fellowship positions for cardiovascular scientists. The day ended with a fun networking event and evening reception, capping a hugely informative, interactive, and enjoyable symposium.



Early Career Scientists networking at a YLS poster session

Meeting Notes

The 'H⁺SSS'ing of Summer Lawns

27–30 July 2013, University of Oxford, UK

Richard Vaughan-Jones

University of Oxford, UK
Deputy President, The Physiological Society

Conference banquet in Hall, Exeter College

The folk/jazz singer, Joni Mitchell, rhapsodised once about the sounds of summer, encapsulated by the hissing of lawn-sprinklers. In July, the lawns of Keble and Exeter Colleges at Oxford were crisping in the summer heat. The H⁺SSS was not of lawn-sprinklers, however, but of H^+ ions being transported within proteins and across cell membranes. The IUPS Satellite Symposium, "H^+ ion Sensing, Signalling and Servo-control" (H⁺SSS, for short), was held in the closing days of July in Oxford, immediately following the main Physiological Congress in Birmingham. These were also the last days before the heat of summer broke in the UK. Indeed, the humidity forced the 65 delegates at the meeting to move to another room, but not before Carol Robinson DBE, FRS (Oxford, UK) had delivered her masterly Plenary Lecture. With remarkable clarity, she led the audience of membrane transport physiologists through the complexities of mass spectrometry, a research field that she has revolutionised. By examining membrane proteins stabilised in a gas phase she has, for the first time, been able to view 3-D multimeric interactions associated with ion pumping by the V-type H^+-ATPase. Despite the summer heat, she held the full attention of her audience. After that, the temperature was taken down, but the scientific quality maintained, by decamping to a cooler lecture theatre. This was Plan B, and fortunately it worked!

The Department of Physiology, Anatomy & Genetics (DPAG) at Oxford played host to the H⁺SSS Conference, organised by Richard Vaughan-Jones (Oxford, UK), and Walter Boron (Cleveland, USA). Accommodation was at nearby Keble College, with a Conference Banquet held at Exeter College. H⁺SSS was the first major gathering for several years of cellular physiologists engaged in the study of intracellular pH regulation, a fundamental cellular control system of major importance in health and disease. Roger Thomas FRS had co-hosted one such meeting at the CIBA Foundation in London in 1987, at premises now occupied by the Academy of Medical Sciences, while Walter Boron hosted another in Snowmass, Colorado in 1996. But apart from important regional meetings in Banff, Canada and Aarhus, Denmark, the field has lacked a recent scientific focus. It was a pleasure, therefore, to see the enthusiasm and rigour that emerged at the international H⁺SSS conference in Oxford.

In addition to the H^+-ATPase discussed by Carol Robinson, there were scientific sessions devoted to the principal membrane transport families involved in cellular and organ acid/base regulation, including Na^+- and Cl^--coupled HCO_3^- transporters, Na^+/H^+ exchangers, and monocarboxylic acid transporters (MCTs). One session focussed on H^+ ion sensing and metabolism by mitochondria, and H^+ ion coupling to intracellular Ca^{2+} and electrical membrane signalling. Other sessions were dedicated to H^+ and HCO_3^- ion fluxes in vascular, intestinal, renal and neuronal systems, as well as in cancer. This latter session represented a re-awakening of major interest in the importance of pH-control to cell proliferation and development.

H⁺SSS was delighted to welcome speakers from nine different countries on three continents, including the USA, Europe and the Far East. Subsequent feedback from delegates who attended the meeting has been very positive. So it is hoped that the "H⁺SSS"ing of summer lawns will not be a faded memory from a lost summer in Oxford. It should be reconvened and re-watered at regular intervals. Volunteers?

With grateful thanks to the Nora Eccles Harrison Cardiovascular Research & Training Institute, Salt Lake City, USA, and B & B Microscopes Ltd, Pittsburgh, USA for funding assistance, and Mrs Mala Gunadasa-Rohling for administrative help.

(L-R) Jochen Deitmer, Mike Romero, Ken Spitzer, Roger Thomas

Carol Robinson answering questions, Richard Vaughan-Jones mediates

Coffee break in Department of Physiology, Anatomy and Genetics

Brain-Heart Interactions in Health and Disease – a symposium in honour of John Coote

21 July 2013, Austin Court, Birmingham, UK

Thelma Lovick

University of Bristol, UK

Those of you who know John Coote, his work and his prestigious and continuing publication output, may be surprised to learn that it is 10 years since his 'retirement'. John has devoted his entire career to physiology via his research interests in the functioning of the autonomic nervous system in health and disease as well as via his teaching. He continues to collaborate actively with research groups in Birmingham, Leicester, Durham, UCL and Oxford and maintains contact with colleagues worldwide.

John has spent 45 years at the University of Birmingham where, following retirement from Head of Department of Physiology in 2003, he now holds the position of Professor Emeritus. It was therefore fitting that more than 130 friends and colleagues from around the globe converged on Austin Court, an attractive canal-side venue in Birmingham city centre, on the day prior to IUPS, in order to honour him and his contribution to physiology.

The theme of the meeting was Brain-Heart Interactions in Health and Disease. Mike White (Birmingham), Roger Hainsworth (Leeds) and James Fisher (Birmingham) started off the day with presentations on the role of muscle afferents, cardiac and pulmonary vascular receptors on different aspects of cardiorespiratory control, drawing from experimental work on animals and humans. The focus then shifted from afferent to efferent regulation when John Townend (Birmingham) described work on the beneficial effects of physical activity and vagal control in humans. A lively presentation by Andre Ng (Leicester) then showed how the innervated *in vitro* heart preparation has been used to great effect in his lab to uncover exciting new developments in the role of nitric oxide in vagally mediated actions on cardiac function.

Moving to the realms of central nervous control of the heart and pathophysiological states, Susan Pyner (Durham) described her work on the anatomical connections of the paraventricular nucleus, and how this circuitry might be implicated in heart failure. Edward Johns (University College Cork) then directed our attention to the cardio-renal axis and how the nervous control of the kidney can play a significant role in the development of hypertension as well as kidney failure. Thelma Lovick (Bristol) showed how the autonomic effects of localised stimulation in the brains of animals are now being translated into the clinical situation; this offers the potential for developing deep brain stimulation in humans to modulate autonomic dysfunction to therapeutic advantage. To close the proceedings David Cechetto (University of Western Ontario) described his studies into the role of the cerebral cortex on cardiac autonomic control which have utilised recordings from sites in various cortical regions of experimental animals and man as well as brain imaging techniques. These studies have shown the importance of the insula, the cingulate and prefrontal cortex in cardiac control.

John Coote

When the formal proceedings had come to an end the party moved for a drinks reception to nearby Bank Restaurant, followed by a convivial dinner and much lively discussion and 'catching up' between friends old and new. The proceedings of this memorable meeting will be published as a special edition of *Experimental Physiology* in early 2014.

The organizer wishes to acknowledge the generous support for the meeting from The Physiological Society, Experimental Physiology (Wiley) and the British Heart Foundation. Thanks also to Kieran Brack, Mary Keen, Zsuzsanna Molnár, Atif Sagir, Attila Sik, and James Winter for their help with the organisation.

Neuroscience 2013

9-13 November 2013, San Diego, California, USA

Nick Boross-Toby & Sally Howells

The Physiological Society

Sunny San Diego was the host to this year's Society for Neuroscience annual meeting. *The Journal of Physiology* booth in the exhibition hall was well positioned in 'Publishers row' and we met a steady stream of neuroscientists who had published in, or reviewed for, *The Journal* over the years.

As ever, the meeting was very well attended, and delegates from all around the world came to learn more about our three journals and The Society. In this online age, researchers were pleased to be able to pick up a free copy of *The Journal of Physiology* to read during the meeting or on their way home. Both *JP* and *EP* had also created virtual issues to coincide with the meeting, which featured the top neuroscience papers published over the past 12 months.

We took the opportunity to play our filmed interviews of *The Journal*'s Consulting Editors, Jonathan Ashmore, Bert Sakmann, David Attwell and Colin Blakemore, which showed *The Journal*'s strength in the field of neuroscience and its close links with world-renowned neuroscientists.

We were pleased to be able to tell people that The *Journal of Physiology* and *Experimental Physiology* are still free to publish in and impose no restrictions on page length or the number of figures that can be included in original research papers – a feature that seems to be increasingly rare in journals publishing.

Several of *The Journal*'s editors were at the event, including Editor-in-Chief, David Paterson. He said: "Once again, The Society for

Reviewing Editor Janet Taylor, Editor-in-Chief David Paterson and Managing Editor Sally Howells at *The Journal*'s stand during SfN's annual meeting.

Neuroscience's annual meeting has been a great success. *The Journal*'s neuroscience issues are building a loyal following and many authors have said how important it is to be published alongside other top neuroscience research."

We have booked our exhibit space for 2014, when the meeting moves to Washington DC, where hats and gloves, not sunglasses and shorts, will be the wardrobe essentials!

Hit the endothelial layer of your skeletal muscle microvessels with HIT to prevent impaired glucose tolerance and chronic disease

The human body, and specifically the microcirculatory system, are sensitive to physical activity or the lack thereof. Health authorities tell us repeatedly that obesity, metabolic syndrome, type 2 diabetes and cardiovascular disease threaten the lives of the sedentary, but few of us manage to meet recommended exercise guidelines. Why is exercise so important to the microvasculature and is HIT really an effective short-cut to maintaining good health?

Anton Wagenmakers & Matthew Cocks

Liverpool John Moores University, UK

An exercise class hitting the endothelial cell layer of the skeletal muscle microvasculature and of feed and resistance arteries with high intensity intermittent training (HIT) on spinning bikes in the health and fitness gym.

The microcirculation in human skeletal muscle is highly responsive to increases and decreases in habitual physical activity with substantial changes in capillary density and activity of endothelial enzymes that control muscle perfusion. Endurance trained athletes combine a high skeletal muscle capillary density with a microvasculature that is highly responsive to meal- and exercise-induced vasodilatation. Individuals that adopt a sedentary lifestyle, including the rapidly growing obese and ageing population, progressively lose muscle capillaries, oxidative capacity and mass. These impairments go in parallel with a high chronic disease risk (metabolic syndrome, type 2 diabetes and cardiovascular disease). This article explains the state of knowledge of the underlying mechanisms and comes to the conclusion that it might be sensible to change your lifestyle, if you do not meet current health authority guidelines. Our advice is to hit your endothelial cells as frequently as possible with brief intense bouts of exercise.

Anatomy of the endothelial cell layer (ECL)

Every blood vessel in the human vasculature is covered on the luminal side with a continuous monolayer of endothelial cells (ECL). The total surface area of the ECL in an adult human has been estimated to cover >700 m^2 and to have a weight of about 700 g (Table 1). This makes the ECL into one of the largest diffuse organs with a significant weight despite the 0.3 µm thickness. The ECL of arteries and veins together covers only about 6 m^2 (Table 1), while the ECL of the microvasculature (arterioles, capillaries and venules) contributes 99% of the total surface area. Of the latter 85% (about 600 m^2) is present in capillaries (Table 1). As skeletal muscle in a 70 kg lean physically active adult has a mass between 35 kg and 40 kg and has a higher capillary density than other tissues (with the exception of the heart), estimates are that at least 400 m^2 of the ECL is present in the skeletal muscle microvasculature, again with the largest surface area in the dense network of capillaries (Wolinsky, 1980). The metabolic rationale behind this distribution is that the ECL in skeletal muscle capillaries is uniquely equipped for the transendothelial transport of nutrients, oxygen and hormones into the interstitial fluid that surrounds the muscle fibres, and that transport capacity depends on the available surface area (Fig. 1). It is assumed that only about 10% of the capillaries in skeletal muscle are perfused in the resting state with large increases in capillary recruitment occurring during high intensity aerobic exercise (Andersen & Saltin, 1977). This additional recruitment during exercise in combination with progressive increases in cardiac output and total muscle perfusion is required to ensure that the supply of blood borne fuels and oxygen meets the high energy demand of the contracting muscle.

General functions of the endothelial cell layer (ECL)

A number of general functions of the ECL are common to all blood vessels (Bakker *et al.* 2009). The ECL by the nature of its location acts as a container for blood in the entire vascular tree. The ECL also acts as a selective barrier preventing the uncontrolled passage of pathogens, molecules and blood constituents that are not supposed to enter healthy cells in our organs and tissues. As such the ECL plays an important role in healthy individuals in preventing leucocytes from binding to the ECL and penetrating into the subendothelial layer where the leucocytes turn into foam cells and form atherosclerotic placques (Wagenmakers *et al.* 2006; Bakker *et al.* 2009). Other mechanisms act simultaneously to rapidly

increase the permeability and available surface area of the ECL in periods of increased metabolic demand. This mostly applies to microvascular transport processes and several examples of this are given in the next section and in Fig. 1. The ECL has also been shown to prevent blood coagulation and the formation of a platelet thrombus and to produce regulators of fibrinolysis (Bakker *et al.* 2009). The luminal surface of the endothelium is covered with a brush like glycocalyx layer (glycoproteins and proteoglycans), which is 0.5 µm thick in capillaries and 4.5 µm in arteries (Reitsma *et al.* 2007; Weinbaum *et al.* 2007). In capillaries it is in direct contact with erythrocytes and leukocytes and acts as a lubricating layer for the narrow passage of these cells (with a diameter similar to the lumen of capillaries). The most important function of the glycocalyx is the translation of haemodynamic forces (shear forces exerted by flowing blood and individual blood cells passing through the narrow lumen of a terminal arteriole) into vasodilatory responses during exercise. As such mechanical forces exerted on the glycocalyx are likely to be early signalling events leading to eNOS activation and the molecular adaptation of the ECL to either increases or decreases in physical activity levels. The glycocalyx is also assumed to protect ECs against shear force-induced damage and in pathological states against damage caused by reactive oxygen species (Reitsma *et al.* 2007; Weinbaum *et al.* 2007).

Role of the ECL in insulin-mediated microvascular dilatation and muscle glucose uptake

Textbooks explaining the role of insulin in whole body glucose homeostasis traditionally assume that activation of the insulin signalling cascade in the skeletal muscle fibres is the main control mechanism (Fig. 2). However, there is now compelling evidence that insulin and glucose delivery to the skeletal muscle interstitium is a conditional early event in skeletal muscle glucose uptake (Coggins *et al.* 2001; Vincent *et al.* 2004; review of Barrett *et al.* 2009). Experiments using contrast-enhanced ultrasound (CEU), an established method which measures the volume of blood present in the muscle microvasculature (primarily in capillaries) and the microvascular blood flow, have shown that physiological increases in insulin lead to rapid increases in the microvascular blood volume in both rat and human skeletal muscle. In rats these increases occur as early as 5–10 min after the start of a physiological insulin infusion and precede both activation of the insulin signalling cascade in skeletal muscle and increases in glucose uptake by skeletal muscle, which are seen after 20–30 min (Vincent *et al.* 2004). This increase in microvascular blood volume has also been observed after ingestion of a mixed meal and during light exercise (Vincent *et al.* 2006). The increase in microvascular blood volume observed in these studies is taken to

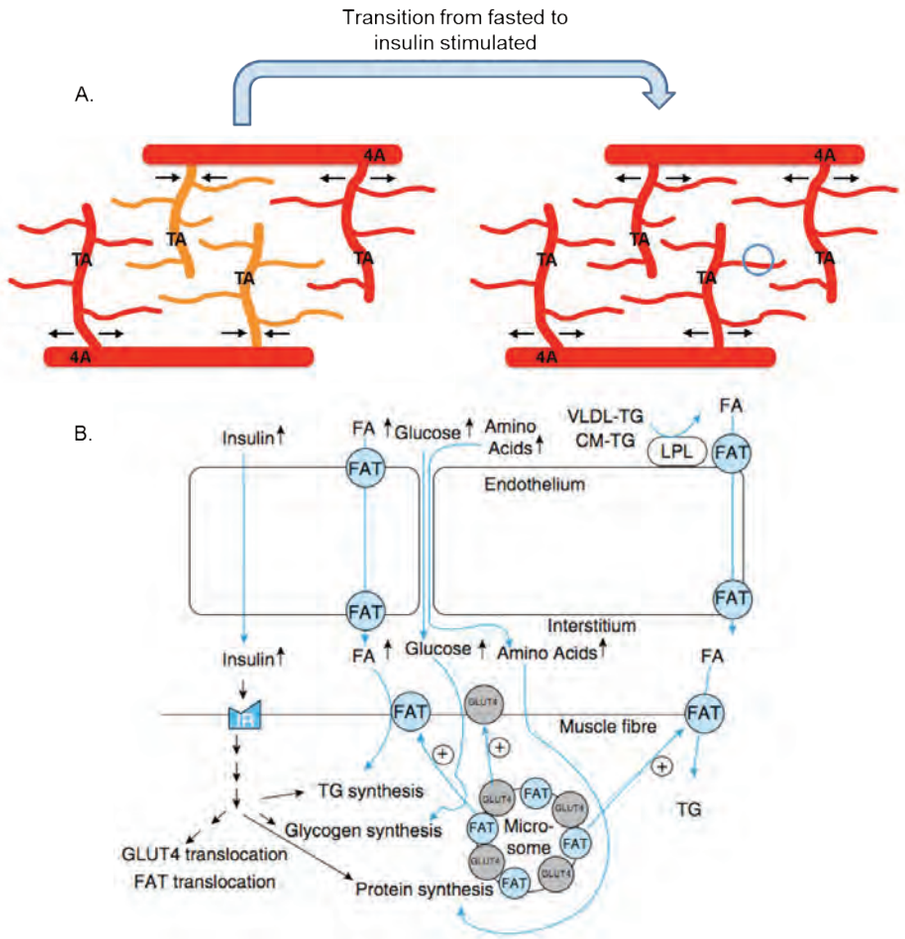


Figure 1. A, Insulin induced vasodilatation of terminal arterioles leads to recruitment of muscle capillaries in the period following meal ingestion. 4A = 4th degree arteriole; TA = terminal arteriole; terminal arterioles supply a series of parallel capillaries with blood. Red blood vessels are perfused with blood; orange blood vessels are underperfused. These underperfused capillaries become fully recruited in response to meal-induced increases in insulin or physiological venous infusions of insulin and this will increase the endothelial surface area that is available for transport of oxygen, insulin and nutrients. The area indicated by the blue circle is enlarged in Figure 1B.

Figure 1. B, Insulin induced vasodilatation of terminal arterioles leads to recruitment of previously underperfused muscle capillaries. As a consequence more insulin, glucose, amino acids and fatty acids (FA) will be transported over the endothelial cell layer of the muscle capillaries and penetrate into the interstitial fluid surrounding the muscle fibres. This then leads to increased uptake of these nutrients in the muscle. The higher concentration of insulin activates the insulin signalling cascade in muscle and leads to translocation of GLUT4 and FAT (fatty acid translocase), and higher rates of amino acid uptake. The higher insulin concentration also leads to an increased stimulation of glycogen synthesis, protein synthesis and triglyceride synthesis. Failure of this recruitment mechanism in insulin resistant states (obesity, type 2 diabetes and cardiovascular disease) leads to high blood concentrations of glucose, triglycerides, amino acids and insulin in the postprandrial period (following ingestion of mixed meals). Note that capillary recruitment increases the access of VLDL-TG (very low density lipoprotein-triglyceride) and CM-TG (chylomicron-TG) to muscle capillary LPL (lipoprotein lipase, which is bound to the glycocalyx of the ECs). Transport processes across the ECL in part are active (against a concentration gradient, e.g. transendothelial transport of insulin) and are, therefore, costing energy. ECs, therefore, have a high capacity to oxidise both glucose and fatty acids. ECs also have a high protein turnover and proliferation rate which serves to replace ECs damaged by shear stress or exposure to oxidative stress (latter in obesity, type 2 diabetes and cardiovascular disease). Reproduced with permission, from Wagenmakers AJM, van Riel NAW, Frenneaux MP & Stewart PM (2006), *Essays Biochem* 42, 193-210. © the Biochemical Society

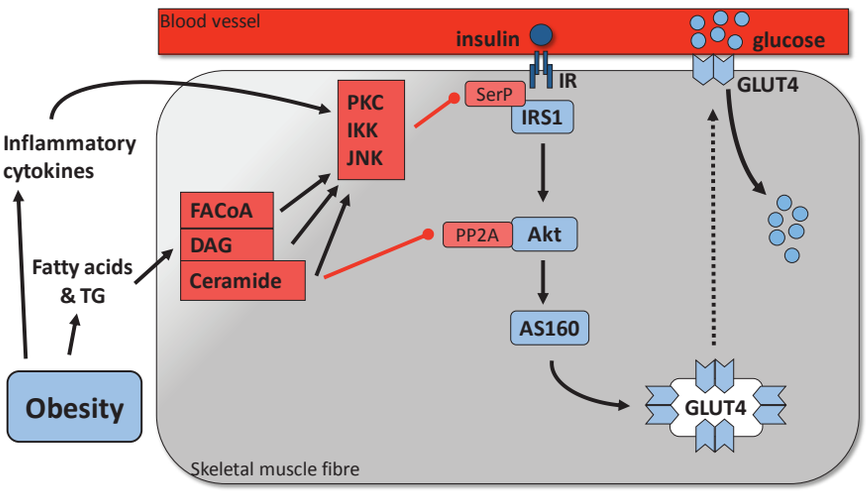


Figure 2. Activation of the insulin signalling cascade in skeletal muscle and impairments that occur in obesity, type 2 diabetes and cardiovascular disease. In healthy trained individuals increases in the insulin concentration in the interstitial fluid surrounding muscle fibres leads to increased activation of the insulin signalling cascade and translocation of GLUT4 (main glucose transporter in muscle) to the plasma membrane. As muscle is the main tissue responsible for glucose uptake in the period after meal ingestion, this will keep the rise in blood glucose concentration following ingestion of a meal relatively modest. As such healthy trained individuals have firm control on their blood glucose levels, both in the fasted period and after food intake. In sedentary obese individuals and patients with type 2 diabetes and cardiovascular disease, high blood levels of fatty acids and triglycerides contribute to an excessive accumulation of lipid metabolites such as long chain fatty acyl-CoA, diacylglycerol and ceramide in skeletal muscle. This together with increased plasma levels of inflammatory cytokines and local inflammation in the muscle microvasculature (see Fig. 3) activates the serine kinases PKC, IKK and JNK. These phosphorylate insulin receptor substrate-1 (IRS1) on serine residues leading to inactivation of IRS1 and downstream inactivation of the insulin signalling cascade. Ceramide accumulation also activates the phosphatase PP2A which dephosphorylates Akt. These mechanisms collectively prevent activation of the insulin signalling cascade in skeletal muscle and, therefore, reduce insulin-mediated GLUT4 translocation and skeletal muscle glucose uptake. Reproduced with permission, from Shaw CS and Wagenmakers AJM (2012), *The Biochemist* 34, 20-23. © the Biochemical Society.

primarily reflect the recruitment of capillaries that were not perfused before. This conclusion is supported by Gudsbjornsdottir *et al.* (2003) using an independent method. The latter study made estimates of the permeability surface area product (PSA) for insulin and glucose in capillaries during an oral glucose tolerance test (OGTT) and physiological insulin infusion. The PSA went up twofold during the OGTT and 11-fold during the insulin infusion, with equal-fold increases seen for skeletal muscle glucose uptake.

The molecular mechanisms leading to insulin-mediated recruitment of previously underperfused capillaries

The mechanisms responsible for insulin-mediated capillary recruitment have remained a puzzle for a long time. Important information has come from studies in cultured ECs (for references see Wagenmakers *et al.* 2006 and Muniyappa *et al.* 2007), which identified an endothelial insulin signalling cascade, activation of which leads to increased production of nitric oxide (NO, Fig. 3). NO produced by the ECL is a potent vasodilator acting upon smooth muscle cells (SMCs)) both in the macro- and in the microvasculature (Wagenmakers *et al.* 2006; Barrett *et al.* 2009). Insulin was found to activate the enzyme endothelial nitric oxide synthase (eNOS) by means of ser^{1176} phosphorylation in cultured rat ECs and ser^{1177} phosphorylation in cultured human ECs. eNOS converts the amino acid L-arginine to the products L-citrulline and NO. Other signals found to activate eNOS via ser$^{1176/1177}$ phosphorylation are fluid shear forces exerted on a cultured EC monolayer and exposure of cultured ECs to vascular endothelial growth factor (VEGF). An important *in vivo* observation made by Vincent *et al.* (2004) was that pre-treatment of rats with the eNOS inhibitor L-NAME prevented the insulin induced increase in microvascular blood volume in skeletal muscle and reduced both glucose uptake and activation of the insulin signalling cascade in skeletal muscle. Collectively these observations led Rattigan *et al.* (2006) to propose that physiological increases in plasma insulin lead to serine phosphorylation of eNOS in the ECL of terminal arterioles in skeletal muscle with the increased NO production leading to relaxation of the VSM cells and dilatation of the terminal arterioles (Fig. 3). As one terminal arteriole supplies a series of capillaries with blood, this will then lead to recruitment of previously underperfused capillaries as explained in the top part of Fig. 1. Although to date, insulin-induced eNOS ser^{1177} phosphorylation has not been observed in the microvasculature of human skeletal muscle, it has been reported in the endothelium of large arteries.

Impairments in the above mechanism lead to insulin resistance and reductions in angiogenesis in obesity and chronic disease

Impairments in insulin-mediated recruitment of skeletal muscle capillaries have been observed in obesity, metabolic syndrome and type 2 diabetes (Keske *et al.* 2009; Barrett *et al.* 2009). Experimental observations made in cultured endothelial cells and the ECL of larger arteries studied either *in vivo* or in arterial rings (for references see Wagenmakers *et al.* 2006) suggest that the underlying molecular mechanisms may involve a reduction in NO bioavailability leading to impaired vasodilatation and are summarised in Fig. 3 and its legend. Apart from these mechanisms the high levels of insulin that prevail in insulin resistant states also activate the MAPK pathway and lead to increases in endothelial expression of endothelin-1 (Muniyappa *et al.* 2007). Endothelin-1 is a potent vasoconstrictor, which will further increase the imbalance between vasodilatation and vasoconstriction, leading to a net reduction in insulin-mediated recruitment of skeletal muscle capillaries. Collectively these mechanisms may explain the substantial reductions that are seen in skeletal muscle glucose uptake during a hyperinsulinaemic euglycaemic clamp both in obese Zucker rats (Wallis *et al.* 2002) and in patients with type 2 diabetes (Gudsbjorndottir *et al.* 2004).

Wagenmakers *et al.* (2006) suggested that the metabolic impairments that lead to reductions in NO bioavailability (Fig. 3) in obesity, chronic disease and ageing may potentially also explain the reduction in the density of the capillary and microvascular network that is seen in these conditions. Evidence in support of this proposal is the experimental observation that eNOS inhibition with L-NNA prevented the angiogenic response to chronic electrical stimulation in rats *in vivo* (Hudlicka *et al.* 2006).

Novel assay to measure muscle microvascular endothelial enzymes

The mechanisms proposed in Fig. 3 are an extrapolation of previously published

observations made in cultured endothelial cells and the ECL of large arteries exposed to insulin, VEGF and fluid shear flow either *in vitro* (arterial rings) or *in vivo*. The protein content and phosphorylation (activation) state of endothelial enzymes in these studies was measured in tissue extracts with Western blot analysis. As it is impossible to isolate capillaries and arterioles from percutaneous human skeletal muscle biopsies, Cocks *et al.* (2012) developed an immunofluoresence microscopy method in which cryosections of human vastus lateralis muscle were stained using antibodies targeting eNOS, eNOS phosphorylated at ser^{1177} and NOX_2 (subunit of NAD(P)H oxidase). Quantification was achieved by analysing fluorescence intensity within the area that stained positive for the microvascular endothelium. This method in the meantime has shown that 1 h of cycling exercise at 65% VO_{2max} significantly increased eNOS ser^{1177} phosphorylation (1.29 ± 0.05-fold change; n = 8 lean sedentary males). A pilot study in lean (LZR) and obese Zucker rats (OZR) also has shown that insulin stimulation during a hyperinsulinaemic euglycaemic clamp led to a significant increase in eNOS phosphorylation at ser^{1176} in the terminal arterioles of the anterior tibialis muscle of the LZR, while a significant decrease was seen in the OZR (Cocks & Wagenmakers, unpublished data).

Impact of various modes of exercise training on metabolic health of the ECL

Traditional endurance training (ET) is recognised as an efficient means to increase eNOS gene expression, protein content and NO production in feeding and resistance arteries (McAllister & Laughlin, 2006), thereby increasing the vasodilatory response to insulin (Barrett *et al.* 2009) and reducing the risk for the development of hypertension and atherosclerosis (McAllister & Laughlin, 2006). ET is also the traditional means to increase the production in skeletal muscle of VEGF, which stimulates angiogenesis via an NO-dependent signal. Recently sprint interval training (SIT; a special form of high intensity interval training (HIT) which requires an exercise cycle ergometer normally only present in specialised exercise laboratories) has received much attention as it was shown to elicit similar muscle metabolic (increases in activity of mitochondrial enzymes, aerobic exercise capacity, intramuscular triglyceride breakdown during exercise and insulin sensitivity) and macrovascular adaptations as ET, despite a marked reduction in time commitment (for references see Cocks *et al.* 2013 and Shepherd *et al.* 2013). Given that the most commonly cited barrier to physical activity is lack of time, it is thought that SIT and HIT may represent an effective strategy to stimulate exercise participation in sedentary individuals. SIT and other forms of HIT, which require access to regular gym equipment such as spinning bikes, may therefore provide a time efficient alternative (requiring only 3 sessions of 20–30 min per week versus 5 sessions of

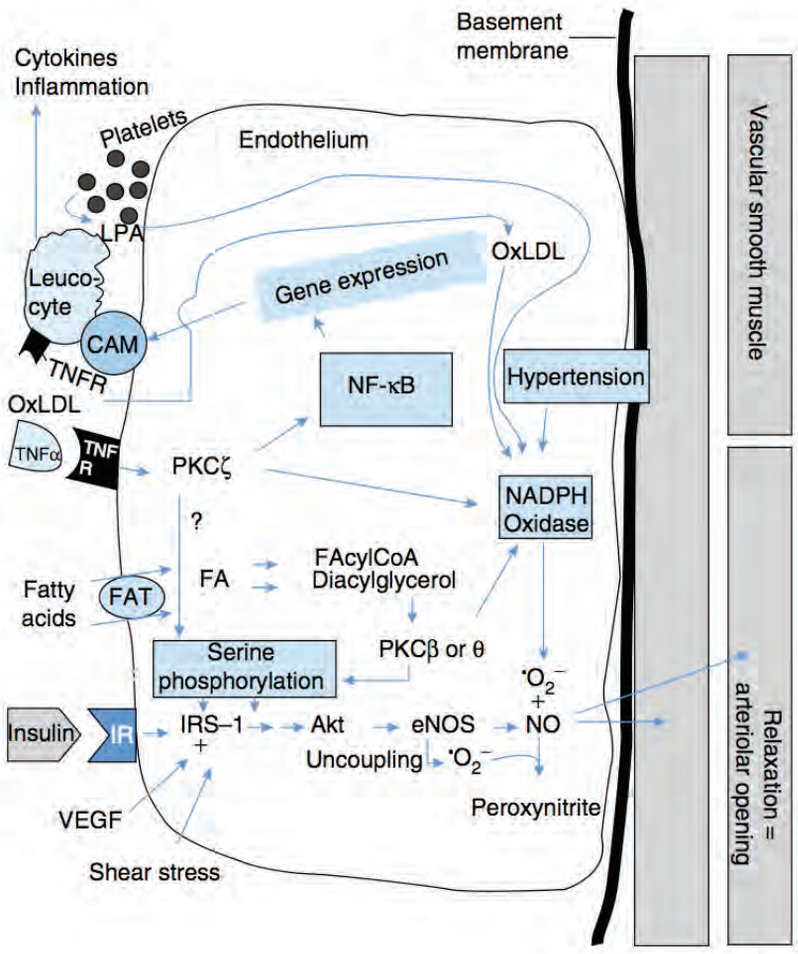


Figure 3. Mechanism by which insulin stimulates NO production and leads to dilatation of terminal arterioles and impairments that occur in obesity, type 2 diabetes and cardiovascular disease. (Note that previous publications have shown that the mentioned mechanisms operate in arteries and cultured endothelial cells; evidence that these mechanisms operate in the ECL of the skeletal muscle microvasculature is not yet complete.) Increases in insulin, VEGF (vascular endothelial growth factor) and exercise induced blood shear stress stimulate endothelial NO production via activation of the insulin signalling cascade in healthy lean physically active individuals. Adoption of a sedentary lifestyle reduces eNOS expression both at the mRNA and the protein level. In obesity, metabolic syndrome, type 2 diabetes, and cardiovascular disease, high concentrations of long-chain fatty acylCoAs and diacylglycerol are seen in the ECL. As in skeletal muscle these fatty acid metabolites activate the protein kinase C isomers, which then phosphorylate IRS-1 on specific serine residues preventing the normal activation of IRS-1 by tyrosine phosphorylation. This prevents activation of Akt and eNOS ser^{1177} phosphorylation and reduces NO production and vascular smooth muscle cell (SMC) relaxation (Naruse *et al.* 2006). Together with the reduction in eNOS protein content, this will reduce insulin-induced NO production and dilatation of terminal arterioles in skeletal muscle. Activation of NADPH oxidase in the endothelium of obese individuals and patients with chronic age-related diseases leads to superoxide anion production, which takes away NO via the formation of peroxynitrite and further reduces NO bioavailability to VSM. High concentrations of inflammatory cytokines activate proinflammatory pathways in skeletal muscle to include NF-κB. This leads to increased expression of cellular adhesion molecules (CAM) playing a role in the binding of leucocytes to the ECL. Secondary cytokines produced by leucocytes and macrophages lead to local inflammation processes in the microvascular wall, attract platelets and destroy the normal endothelial barrier function among others leading to the uptake of oxLDL (oxidized low density lipoprotein), which contains lysophosphatidylcholine, a known activator of NADPH oxidase. The platelets produce lysophosphatidic acid (LPA), another signal molecule that activates NADPH oxidase. Hypertension activates NADPH oxidase via mechanisms involving both increases in angiotensin II and increased strain. Finally the enzyme eNOS itself can produce oxygen free radicals via uncoupling due to a low availability of its cofactor tetrahydrobiopterin. IR, insulin receptor; TNFR, TNF-receptor; FAT, fatty acid translocase. Reproduced with permission, from Wagenmakers AJM, van Riel NAW, Frenneaux MP & Stewart PM (2006), *Essays Biochem* 42, 193-210. © the Biochemical Society. Supporting references are given in the original source.

40–60 min per week in traditional ET protocols) to increase muscle capillary density and protein content of eNOS. To test this hypothesis Cocks *et al.* (2013) have used the novel immunofluoresence microscopy method described above to compare the effects of 6 weeks of ET versus SIT. SIT was found to be as effective as ET in increasing muscle capillary density and insulin sensitivity, while SIT increased the skeletal muscle microvascular eNOS content significantly more (36%; $P < 0.05$) than ET (14%).

Health advice to maintain a life-long healthy ECL

This article comes to the conclusion that the endothelial cell layer (ECL) of the skeletal muscle microvasculature plays a major role in the mechanisms that control skeletal muscle glucose uptake in health and disease (to include obesity, metabolic syndrome, type 2 diabetes and cardiovascular disease). Our recent study (Cocks *et al.* 2013) in lean, healthy, but sedentary young men, comes to the conclusion that the ECL of the skeletal muscle microvasculature is extremely sensitive to 6 weeks of ET and SIT with measurable increases in capillary density, eNOS protein content and insulin sensitivity. The current exercise guidelines of the WHO, American College of Sports Medicine and UK Department of Health are to participate for minimally 150 min per week in moderate intensity endurance exercise, which by many is regarded as being an unrealistic target. Therefore, our advice to the readers of this article who fail to meet this target despite trying hard is to hit the endothelial cell layer of your skeletal muscle microvessels with HIT to prevent impaired glucose tolerance and chronic disease in the future. The excuse that your job and personal life are so demanding that there is not enough time for exercise is no longer valid and the price paid in later life for not making time today will be very high.

	Endothelium		Smooth muscle
	Surface area (m^2)	Weight (g)	Weight (g)
Aorta	0.016	0.016	31
Large arteries	0.33	0.33	330
Small arteries	1.45	1.45	290
Arterioles	26.1	26.1	497
Capillaries	600	600	None
Venules	88.0	88.0	352
Small veins	3.27	3.27	163
Large veins	0.68	0.68	342
Vena cava	0.018	0.018	27
Total for vascular tree	719	719	2032

Table 1. Estimated surface area and weights of the vascular tree in a 70 kg man. This table is adapted using data from Wolinsky (1980).

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The unique and important role of the myogenic response in the lymphatic system

The lymphatic system provides a critical function, preventing lymphoedema from which 200 million individuals worldwide suffer. Current therapies lack efficacy due to our poor knowledge knowledge of how lymphatic muscle works, including the mysterious role of the myogenic response.

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The lymphatic system consists of networks of interconnected capillaries, collecting vessels and lymph nodes that absorb, collect and transport the fluid and protein filtered from the blood vascular system (Levick & Michel, 2010). This system provides a critical homeostatic function: in humans, lymphatic vessels return >4 litres of fluid and a substantial amount of protein per day back into the great veins of the neck. Lymphatic vascular dysfunction results in the accumulation of excess fluid (oedema) in the interstitium. Although oedema is typically not life-threatening, it has serious health consequences, including pain, immobility, fibrosis, inflammation, adipose tissue accumulation and tissue damage. Because the lymphatic system is also a critical component of immune responses, lymphoedema is almost always accompanied by an increased risk of infection and other immune system problems (Rockson & Rivera, 2008).

Lymphoedema affects over 200 million people worldwide. Whereas many types of congenital lymphoedema are caused by mutations in genes controlling lymphatic vessel development (Rockson & Rivera, 2008; Alitalo, 2011), the majority of lymphoedema cases in developed nations are acquired secondary to some other type of disease process, such as obesity (Greene *et al.* 2012; Weitman *et al.* 2013), congestive heart failure (Witte *et al.* 1969; Leduc *et al.* 2011) and peripheral artery or venous disease (Rockson, 1998; Rockson & Rivera, 2008). The largest percentage of cases of acquired lymphoedema, numbering 10–20 million, are patients who develop lymphoedema secondary to breast cancer therapy, recurrent infections, trauma or vascular surgery (Szuba *et al.* 2003). Symptoms may appear within days or be delayed for years, but ultimately lymphoedema afflicts approximately half of breast cancer survivors who have undergone axillary lymph node dissection (Armer, 2005). There is no cure for lymphoedema and the usual treatment options – massage and/or external compression – only temporarily alleviate symptoms rather than address the underlying cause, which in most instances involves lymphatic tract disruption and/or compromised lymph pumping (Modi *et al.* 2007; Stanton *et al.* 2009).

The anatomy of the lymphatic system is key to understanding its function. Lymphatic capillaries interweave among blood capillaries in almost all tissues. The two types of vessels do not normally interconnect; thus lymphatic vessels are nearly invisible due to the absence of lumenal red blood cells (RBCs) (Fig. 1A). Lymphatic capillaries are composed of a single layer of overlapping/interdigitating endothelial cells with discontinuous tight junctions that allow one-way entry of fluid from the tissues. These capillaries eventually coalesce to form collecting lymphatics with a defined basement membrane, at least one muscle cell layer and discrete, one-way intraluminal valves. The muscular collecting lymphatics perform the majority of the work involved in transport through the lymphatic vasculature.

In contrast to the blood vascular system, where the pumping action of the heart generates a pressure head that drives blood 'downhill' through arteries, arterioles and capillaries to the venous side of the circulation, the lymphatic system does not rely on this pressure head to move lymph. Instead, in regions of the body below the heart, lymph is propelled 'uphill' against a pressure gradient. As illustrated in Fig. 1B, which summarizes one of very few studies measuring the pressure gradient within an

intact lymphatic network, the pressure in lymphatic capillaries (or terminal lymphatics (TLs)) is very close to interstitial tissue pressure (~0 cmH_2O). Further downstream (i.e. centrally), just before the collecting lymphatics enter a lymph node, the pressure can exceed 15 cmH_2O (Zweifach & Prather, 1975). The addition of a hydrostatic column associated with upright posture in a biped would accentuate this gradient. Movement of lymph against this adverse pressure gradient occurs by two mechanisms: (1) the spontaneous, rapid contractions of the smooth muscle cells in the walls of collecting lymphatic vessels, as reflected by the oscillations in intraluminal pressure shown in Fig. 1; or (2) passive compression of the thin-walled lymphatic vessels by external forces, such as might occur with skeletal or visceral muscle contraction. One-way lumenal valves, spaced every few millimetres (in rodents) or centimetres (in larger species) serve the critical function of preventing backflow so that net lymph movement proceeds centrally. Valve opening and closing occur passively in response to the pressure gradient across the valve. The pumping unit, called a lymphangion, is represented by the lymphatic vessel segment bounded by two valves, with one allowing inflow to fill the pump and the other preventing backflow following the ejection of lymph associated with a single pump cycle.

In contrast to common misconceptions, external compressive forces normally account for less than one-third of normal lymph movement in humans, whereas active pumping accounts for over two-thirds (Olszewski, 2002). Indeed, in chronic human lymphoedema, observations of collecting lymphatic vessels in the dependent extremities of patients suggest that the 'overloading of lymphatics with an excess of continuously produced lymph brings about dilatation of vessels with subsequent insufficiency of unidirectional valves [and] ... retrograde flow; the stretched lymphatics ... do not generate effective pressures sufficient to propel lymph' (Olszewski, 2002). It is notable, and unfortunate, that all current therapies for lymphoedema utilize passive compression to promote lymph movement rather than targeting the active lymph pump. This is in large part due to our lack of knowledge of how lymphatic muscle works and how it might be targeted therapeutically.

Work in our laboratory focuses on the role that the muscular, collecting lymphatic vessels play in propelling lymph. To study these vessels under defined conditions, we isolate lymphatic segments from either rat or mouse, cannulate them using micropipettes, and connect them to a two-channel servo system to independently control inflow and outflow pressures. Intraluminal pressure is measured using a servo-null micropipette, internal diameter by edge detection and valve positions by densitometry (see Fig. 2A). We

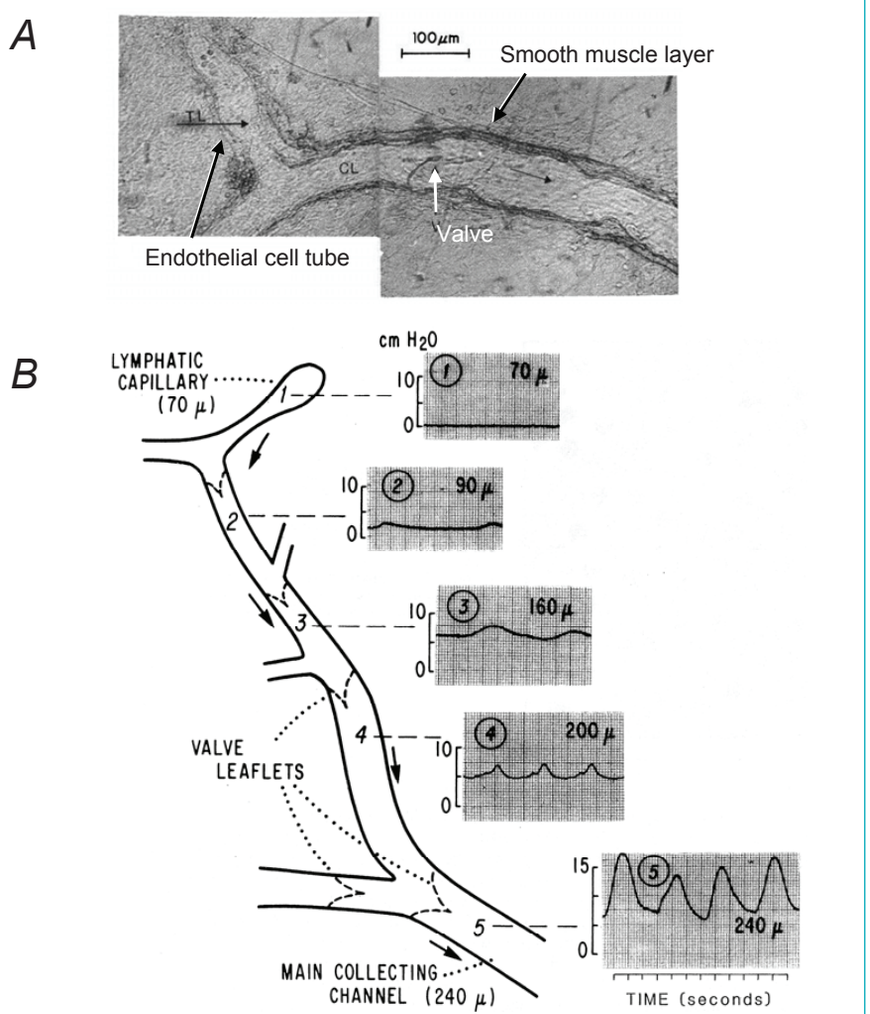

Figure 1. A, photomicrograph of a terminal lymphatic (TL) and collecting lymphatic (CL) in the rat mesentery. B, pressures measured in sequential segments of the rat mesenteric lymphatic system show that lymph moves against an adverse pressure gradient. A modified from Hargens & Zweifach (1977), B from Zweifach & Lipowsky HH (1984).

can study segments with a single valve, two valves (a complete lymphangion) or multiple valves (chains of lymphangions). In a series of studies performed over the last 10 years, we have found remarkable similarities between the behaviour of lymphatic muscle and both cardiac muscle (Muthuchamy *et al.* 2003; Davis *et al.* 2012; Scallan *et al.* 2012b; Zhang *et al.* 2013) and vascular smooth muscle (Gashev *et al.* 2002; Davis *et al.* 2009).

The myogenic response of lymphatic vessels is particularly intriguing and will be the focus of the rest of this article. Normally, arterioles respond to an increase in intravascular pressure with constriction and to a decrease in pressure with dilatation; this intrinsic (myogenic) response of arteriolar smooth muscle is likely to aid in protecting capillaries from pressure overload (Davis, 2012). Lymphatic vessels have been known for a long time to react with extreme sensitivity to increases in luminal pressure by increasing contraction frequency (Smith, 1949) and, over a limited pressure range, by increasing contraction amplitude (Zhang *et al.* 2007).

Our laboratory was the first to show that they also exhibit myogenic constrictions, such that when both inflow and outflow pressures are elevated simultaneously (in the absence of flow), the vessels initially distend, but secondarily develop an increase in basal tone over time (Davis *et al.* 2009). This response is not only similar in pattern and time course to that of many arterioles, but is comparable in magnitude on a per-unit-pressure basis.

Until recently it has been difficult to envision a homeostatic role for the lymphatic myogenic constriction. In response to pressure elevation, which might occur either as a result of increased lymph formation, partial obstruction of the outflow tract, or elevation in body position, constriction would increase outflow resistance and further retard lymph flow. However, the findings reported in our recent paper in *The Journal of Physiology* (Scallan *et al.* 2012a) shed new light on this phenomenon and its potential physiological importance. Instead of elevating both input and output pressures simultaneously as in previous studies, we selectively raised output

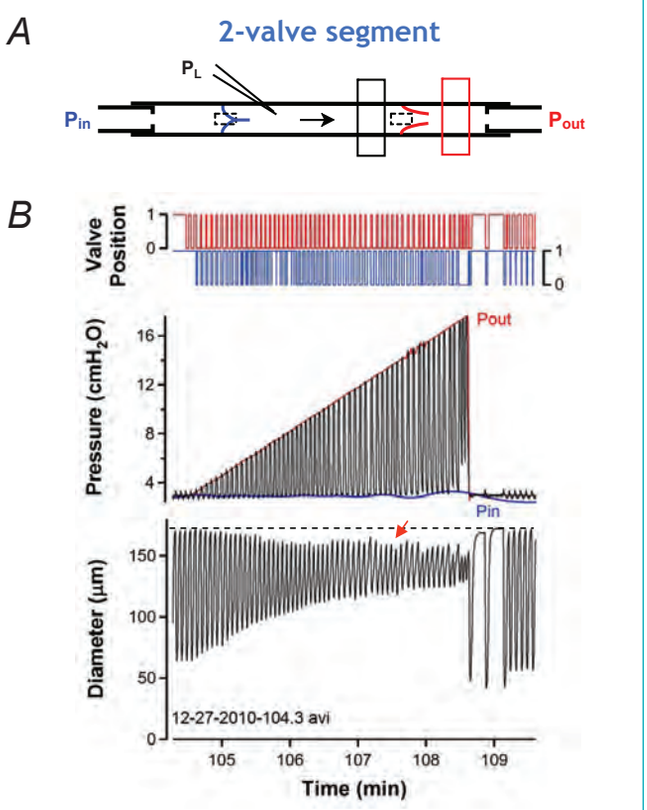

Figure 2. A, diagram of the isolated rat lymphangion showing where measurements of pressure, diameter and valve positions are made. B, normal response of an isolated lymphangion to a ramp-wise increase in output pressure. Red arrow indicates constriction of the segment on the upstream side of the output valve.

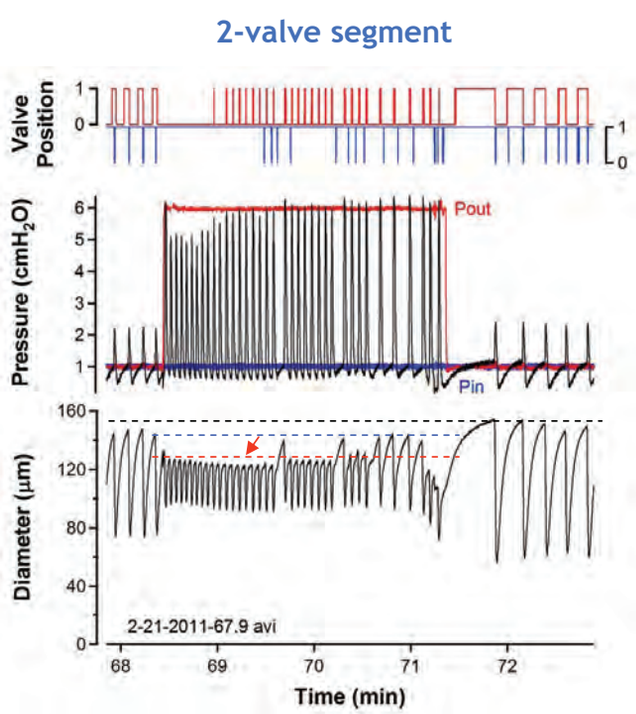

Figure 3. Response of an isolated lymphangion to a step increase in output pressure. An immediate increase in the frequency of spontaneous contractions occurs. The difference between the black and blue dotted lines indicates the component of constriction induced by pressure whereas the difference between the blue and red dotted lines indicates the component of constriction resulting from the frequency change.

pressure to a single lymphangion isolated from the rat mesentery, while measuring pressure and diameter in the segment between the two valves (Fig. 2A). Under these conditions the output valve closes and prevents direct transmission of pressure back into the lymphangion. Nevertheless, the vessel responds with a progressive constriction as output pressure is raised in a ramp-wise manner (Fig. 2B). The bottom trace shows the change in diameter, which is alternating during each contraction cycle between a maximum (end-diastolic diameter, EDD) and a minimum (end-systolic diameter, ESD). The middle trace shows the intraluminal pressure change between the two valves: in systole, pressure rises (due to contraction of the muscle layer) to a value that just exceeds the output pressure, P_{out}, resulting in the opening of the output valve (top trace, red) and ejection; in diastole, pressure falls to a value approximating the input pressure, P_{in}, allowing the lymphangion to fill from the input pipette when the input valve (bottom trace, blue) opens. A constriction is evident as a decline in EDD (red arrow, compare to dotted reference line). Two factors account for the constriction, the first a myogenic response and the second an increase in contraction frequency. Even though the closed output valve prevents backward transmission of output pressure, a myogenic response occurs because of an increase in time-averaged mean pressure inside the lymphangion (approximately equal to 1/3 of P_{out}). An increase in frequency dictates that there is less time for filling in diastole, therefore limiting the filling-induced rise in EDD. The vessel shown in Fig. 2B does not show the frequency component because frequency was already elevated at the start of that protocol (the largest change in frequency typically occurs between pressures of 0.5 and 3 cmH_2O and that protocol started at 3 cmH_2O).

The combination of a myogenic constriction and the effect of a frequency increase induced by output pressure elevation is more clearly evident in vessels starting the protocol at a lower baseline pressure and thus at a lower spontaneous contraction frequency (see Fig. 3). In this example output pressure was elevated step-wise from 1 to 6 cmH_2O, to illustrate that a frequency increase can begin during the first contraction cycle following the step. While output pressure remains elevated, frequency remains high, except for six spontaneous pauses that occur; during each of these pauses EDD rises to a value that is intermediate between its initial level prior to P_{out} elevation and its level during the first cycle after P_{out} elevation. The component of constriction due to the frequency increase is represented by the difference between the dotted blue and red lines whereas the component due to pressure-induced constriction is represented by the difference between the dotted black and blue lines.

What triggers the increase in contraction frequency in response to elevated output pressure? One-valve segments allow us to separate the myogenic and frequency components of the response because when output pressure is elevated the valve closes and stays closed and pressure on the input side remains at a level near the input pipette pressure (except for very small spikes associated with contractions). The black diameter trace in Fig. 4 shows that a progressive constriction (black arrows) occurs on the input side as P_{out} is elevated to increasingly higher levels. This constriction is mediated entirely by an increase in frequency, which is initiated on the output side of the valve. The overlaid red diameter trace (offset for clarity) reveals that the output segment actually distends during each P_{out} step and exhibits a small, secondary myogenic constriction (red arrow, compare EDD to the dotted reference line). The segments on both sides of the valves exhibit synchronized contractions; moreover, the entire vessel segment is synchronized to contract at the highest frequency of any given region. Thus, in response to P_{out} elevation, the segment on the output side of the valve is distending, increasing its contraction frequency and showing a myogenic constriction (but

nevertheless a net dilatation), while pacing the segment on the input side of the valve to also contract at the higher frequency. The input segment undergoes a net constriction because the higher frequency restricts the time for filling during diastole. Subsequently, we used inhibitors, applied selectively to the output side of the segment, to show that the output segment drives the input segment through a signal, probably electrical, that is conducted along the vessel wall across the valve.

Finally, observations made using two-valve segments provide clues as to why pressure-induced constriction might be physiologically advantageous to the lymphangion. When lymphangions are subjected to increasingly higher levels of output pressure, they show a combined myogenically and frequency-induced constriction initially, but at some point that constriction begins to wane. An example is shown in Fig. 5, where diameter is measured just upstream from the output valve and the constriction wanes at the vertical dotted line. As the input side of the valve loses tone (due to the selective loss of myogenic constriction as frequency remains elevated), the input valve ceases to open (blue valve trace) and diastolic pressure no longer returns to its control value (blue line, equal to P_{in}), but gradually begins to rise with each subsequent contraction cycle. After about 1 min, pressure equilibrates rapidly across the output valve in the middle of systole, giving the appearance of the valve locking open ('lock'). In separate studies we demonstrated that when pressures equalize across a valve it reverts to its default position, which is open (Davis *et al.* 2011). The output valve is not damaged under these conditions because normal function of the valve can be restored by lowering output pressure. However, if output pressure remains elevated this sequence of events has disastrous consequences for the lymphangion because the pump shuts completely down and output pressure is transmitted upstream to the input valve. In chains of lymphangions, we have observed this phenomenon propagate throughout the whole chain until all but one of the valves is 'locked open' (unpublished observations). If this sequence leads to transmission of output pressure back to the lymphatic capillaries *in vivo*, the consequence would be to retard fluid absorption from the interstitium into the lymphatic capillaries and thereby exacerbate oedema formation. Pressure-induced constriction therefore appears to protect the lymphatic valves from becoming overdistended and temporarily insufficient, as well as to protect the lymphatic capillaries from backward pressure transmission.

In conclusion, our studies of single, isolated lymphangions under defined pressure conditions show that collecting lymphatic vessels constrict by a combination of two mechanisms when exposed to elevated output pressure: (1) a pressure-dependent myogenic constriction, and (2) a pressure-induced increase in contraction frequency that leads to a reduction in filling time and decline in diameter. Combined, these two effects produce a stronger constriction (on a per-unit-pressure basis) than myogenic constrictions observed in many arterioles. When pressure is increased at the output end of a lymphatic segment, closure of the closest valve protects the rest of the vessel from the full force of the pressure rise; nevertheless the segment on the upstream side of the valve constricts because the output segment responds with an increase in frequency that drives synchronized contractions of the entire segment at that higher frequency. Although pressure-induced constriction may increase outflow resistance, this deleterious effect on lymph transport may be offset by a need to protect valve regions from becoming overdistended and the valves insufficient.

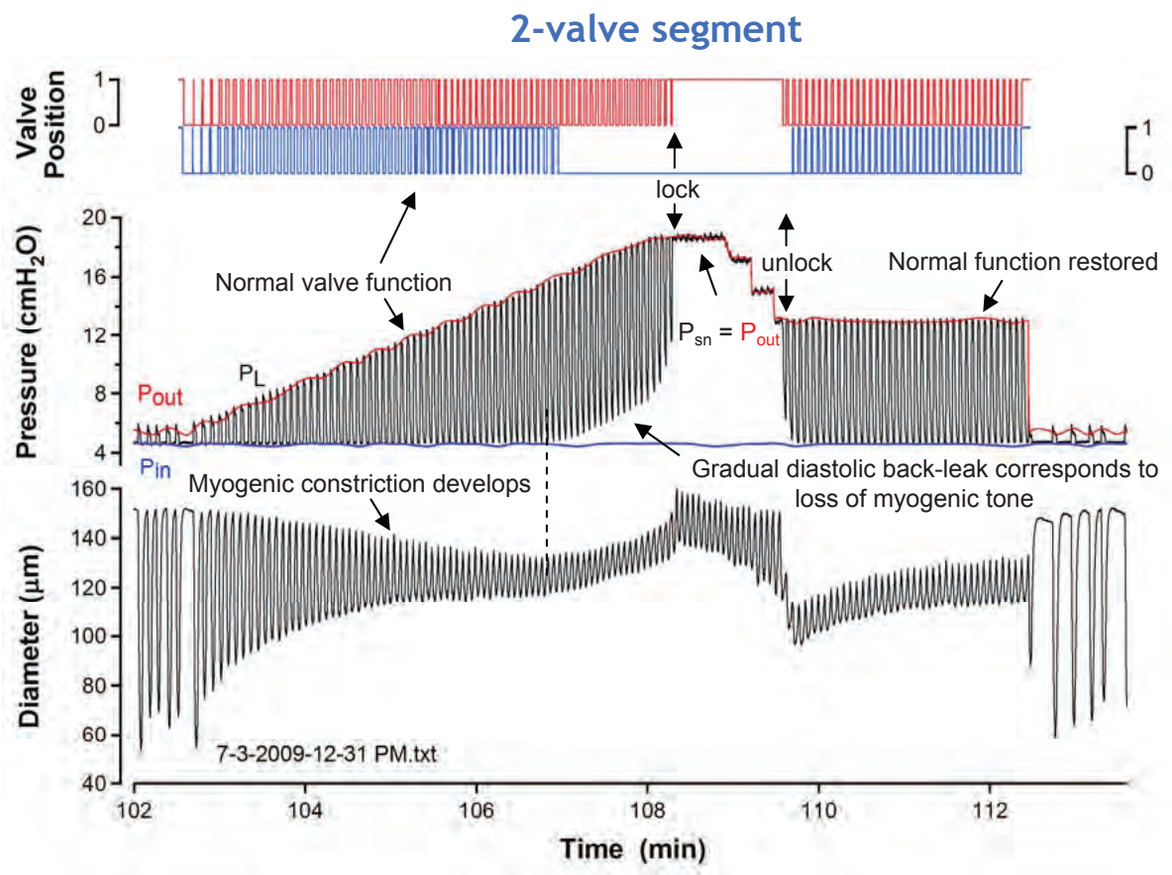

Figure 4. Response of a one-valve segment to a step increase in output pressure. The pressure on the upstream side of the segment is not allowed to change, so the constrictions (black diameter trace) are due entirely to changes in frequency, which is controlled by the downstream segment (red diameter and pressure traces).

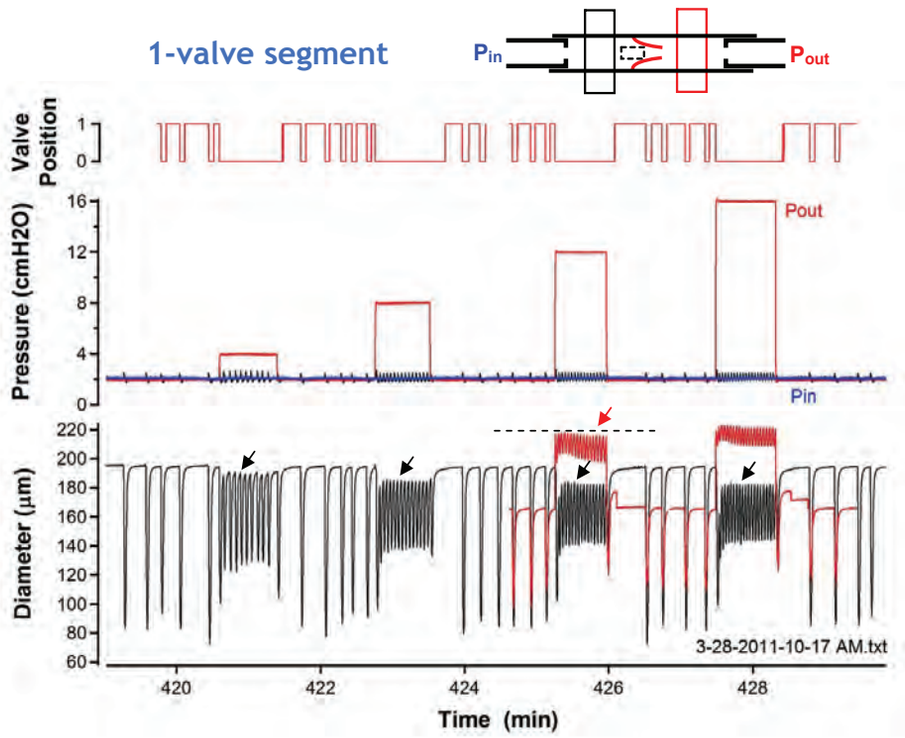

Figure 5. A lymphangion that undergoes valve dysfunction when the upstream segment loses myogenic tone at higher levels of output pressure. See text for explanation.

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Physical activity for physiologists

Our understanding of the physiological changes which take place during exercise and physical activity has improved enormously over the past few decades, but physiologists are missing out on the opportunity to get even more out of their research.

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Human physiologists spend a great deal of time characterising their participants in research studies with sophisticated and often highly expensive measures to get a better understanding of their 'subjects'. However, there is very little effort to characterise physical activity and, instead, participants are usually loosely described using terms such as 'sedentary', 'recreationally active' or something similar. This is hampering future progress.

The terms 'exercise' and 'physical activity' were carefully defined almost 30 years ago but physiologists still tend to use the terms interchangeably. According to these definitions, physical activity represents any movement or force that increases energy expenditure above rest whereas exercise is a subcomponent of physical activity that is structured or planned (Caspersen *et al.* 1985). This is not just splitting hairs – whilst physiologists may be satisfied that participants will be able to tell them about their exercise participation this is missing something much more important – physical activity energy expenditure.

Some people may tell you that they are sedentary when this is clearly not the case

Figure 1 shows physical activity energy expenditure for four different middle-aged men described in more detail elsewhere (Thompson *et al.* 2012). One of these (B) has engaged in structured exercise with prolonged bouts in the morning and evening. The others have engaged in no exercise but nonetheless show enormous variability in physical activity energy expenditure. As physiologists, would we expect A to respond to either acute exercise or an exercise/physical activity intervention in the same way as C or D? Would we expect D, with an equivalent Physical Activity Level or PAL (total energy expenditure/resting metabolic rate) to B, to appear equivalent from a physiological perspective? I suspect not – and yet this is rarely considered even though we now have the technologies to do so.

An exercise 'prescription' represents a supplementary stimulus

Even a person with a very low level of activity in the sedentary range (e.g. a PAL of 1.30) expends several hundred kilocalories a day through physical activity (Brooks *et al.* 2004). This is similar to the energy expended in walking several miles. Crucially, PAL can vary enormously even without the participation in structured exercise. Thus, when exercise is prescribed to elicit a given physiological response, we should not assume that the baseline is zero. Figure 2 shows the extent with which structured exercise acts as a supplement to other physical activity. In this study, at week 18 of the intervention, participants were engaging in a significant amount of prescribed exercise (almost 4 hours of exercise per week at 65% of their maximum oxygen uptake), and yet this only represented 15% of physical activity energy expenditure (Turner *et al.* 2010). We should

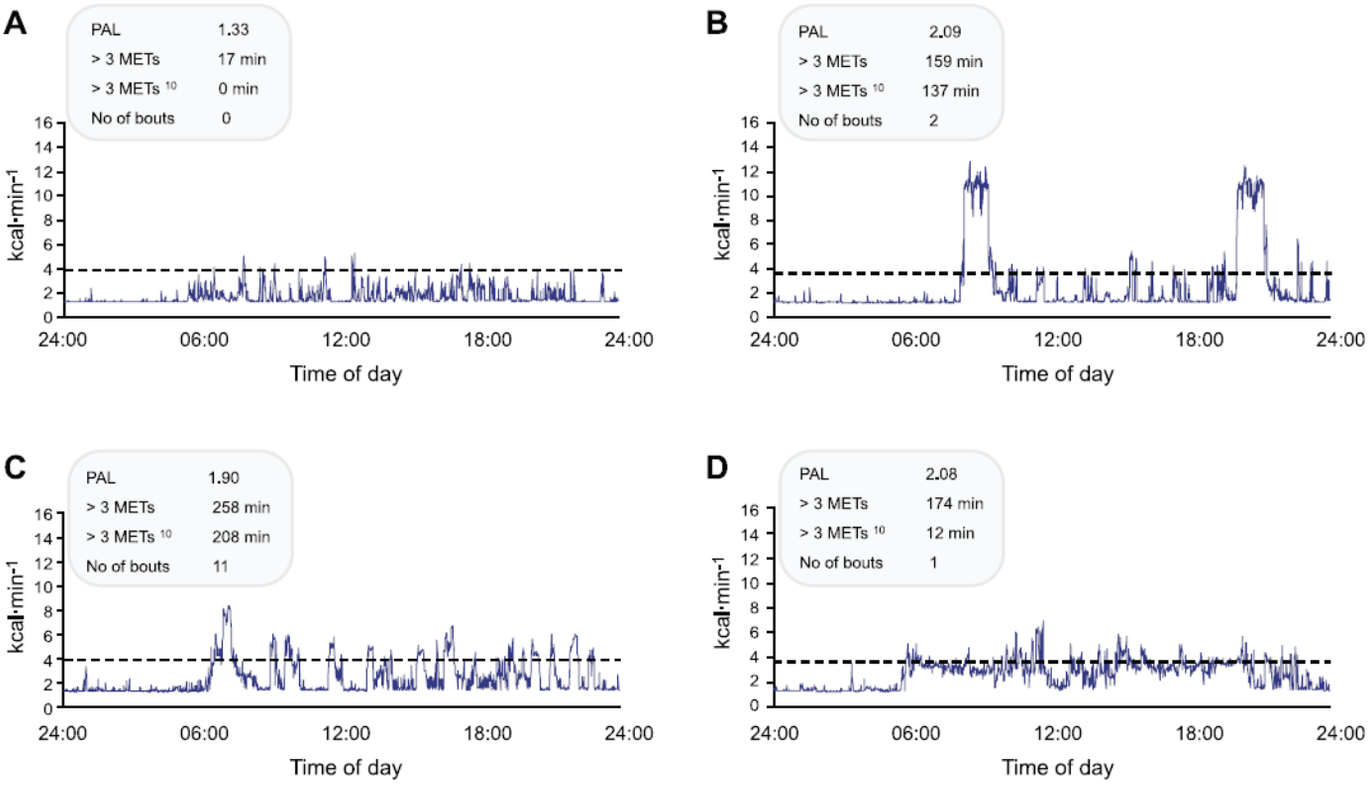

Figure 1. Physical activity energy expenditure over a 24 h period in four different middle-aged men (Thompson *et al.* 2012). Physical Activity Level (PAL) is the product of total energy expenditure/resting metabolic rate. METs represent metabolic equivalents where one MET is equivalent to resting metabolic rate.

ask ourselves, which is the greatest physiological stimulus at this time – the supplementary prescribed exercise or all the other physical activity energy expenditure which existed before the intervention? Certainly, there is strong evidence that low level physical activity is enormously important for many different outcomes (Levine *et al.* 2006; Hamilton *et al.* 2007), with perhaps some of the best evidence coming from studies showing profound physiological changes when it is taken away (Thyfault & Krogh-Madsen, 2011; Breen *et al.* 2013). Thus, it is clear that exercise cannot be treated in the same way as with the introduction of a new drug (i.e. absent before prescription) since 'new' exercise only supplements existing (variable) physical activity.

We need to explore the impact of variability in physical activity on physiological outcomes

Variation in habitual physical activity may contribute to some of the variability in response to traditional exercise interventions. The HERITAGE Family Study is a wonderful study which illustrates some of the potential variability in response to a standardised exercise prescription (Bouchard

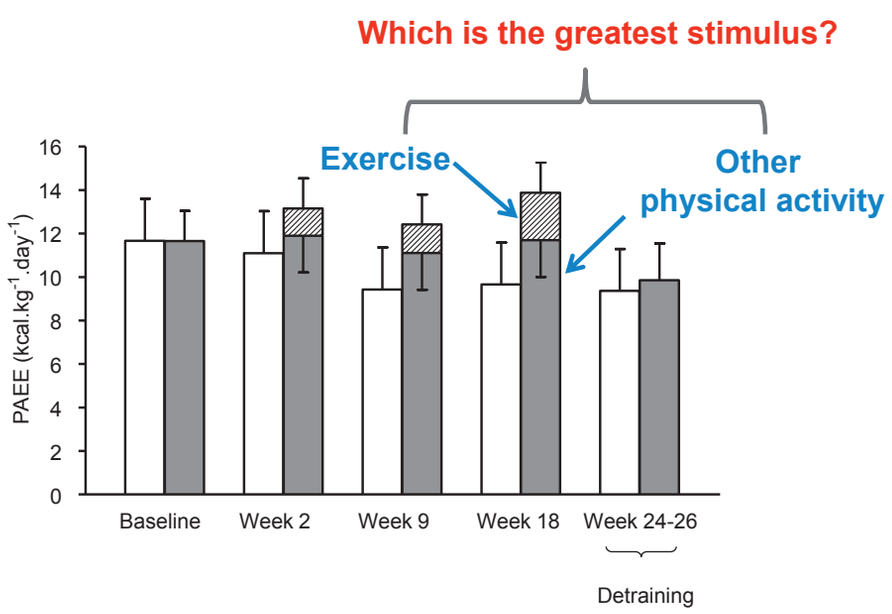

Figure 2. Which is the greatest physiological stimulus – physical activity or exercise? These data show physical activity energy expenditure (above rest) during a traditional exercise intervention (Turner *et al.* 2010). By week 18, participants were exercising four times a week for approximately 50 mins each time at an intensity of 65% maximum oxygen uptake – and yet this represents only ~15% of physical activity energy expenditure. Open bars show the control group. Shaded bars show non-prescribed physical activity energy expenditure and hatched bars show energy expenditure during prescribed exercise.

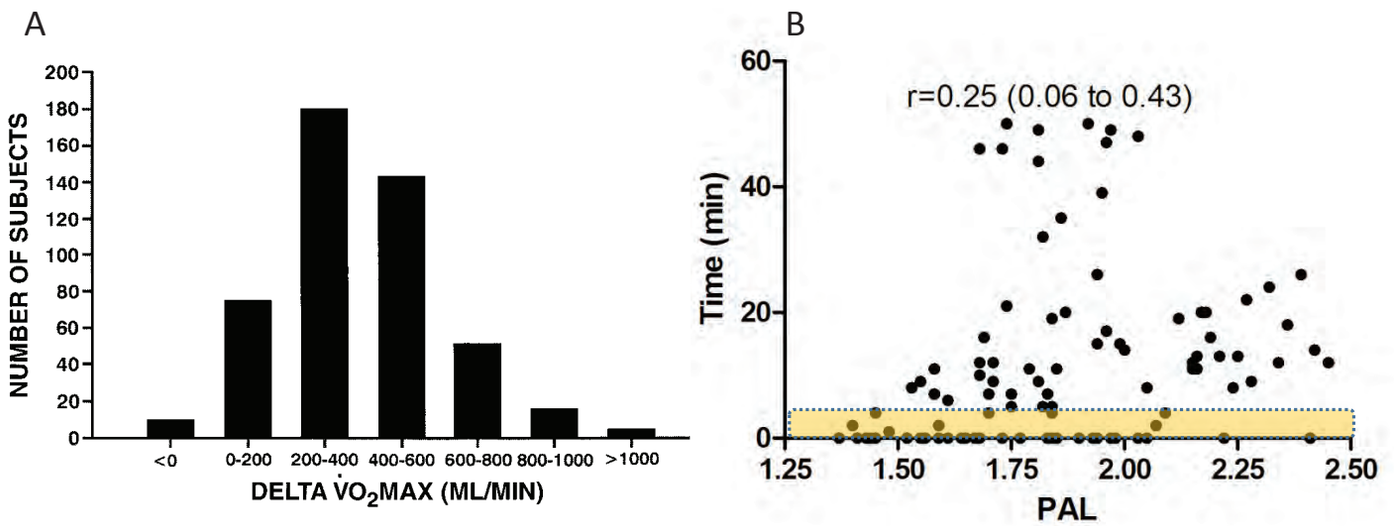

Figure 3. Variability in physiological responses to an exercise intervention alongside variation in habitual physical activity energy expenditure. A, variability in changes in maximum oxygen uptake as shown in the HERITAGE study (Bouchard *et al.* 1999); B, the relationship between time engaged in physical activity above 7.2 METs (similar to the threshold used to recruit participants to HERITAGE) expressed against PAL (Thompson & Batterham, 2013). The people in the orange shaded box in panel B would be included in studies such as HERITAGE but clearly there is enormous variation in PAL (ranging from physical activity energy expenditure of a few hundred kilocalories to more than 2000 kilocalories per day).

et al. 1999). It is worth noting that in HERITAGE participants were recruited based on self-reported participation in physical activity greater than 7 or 8 METs (depending on age). This is perfectly reasonable given the techniques that were available in the 1990s. However, as shown in Fig. 3, it is quite possible that some of the variability in training-induced outcomes such as maximum oxygen uptake reflects variation in pre-training habitual physical activity below this 7 or 8 MET threshold. For some individuals, prescribed exercise in HERITAGE will have reflected an enormous supplement and in other cases it will have been tiny in comparison to all their other physical activity energy expenditure. Since this pre-existing habitual physical activity has a major impact on maximum oxygen uptake, insulin sensitivity, postprandial skeletal muscle protein synthesis and so on (Thyfault & Krogh-Madsen, 2011; Breen *et al.* 2013), then we cannot know how much of the documented inter-individual variability in HERITAGE reflects variability in baseline pre-intervention physical activity. Of course, this is likely to be outcome specific and will not be the same for all physiological parameters. However, if we want to separate out true biological variability, we should capitalise on technological innovation and account for any variability in a given response that has been introduced because of inter-individual variability in pre-intervention habitual physical activity.

Exercise substitutes for other physical activity

Prescribed exercise in traditional intervention studies will rarely replace absolute rest and instead substitutes for other physical activity. Variability in habitual physical activity will affect the degree of substitution. Indeed, for an individual with a relatively high level of baseline physical activity, it is quite possible that a modest exercise prescription simply substitutes for similar intensity non-exercise physical activity. It is therefore unsurprising that prescribed exercise interventions do not always lead to an increase in overall energy expenditure or supplement other physical activity whatsoever (Goran & Poehlman, 1992). A more careful characterisation of the physical activity of our participants will help us to compare the results between studies in order to understand the impact of our interventions.

The picture gets uncomfortably complex ...

This might already seem complicated enough but, unfortunately, the picture becomes even more complex. For example, using the same robust data for physical activity energy expenditure, approximately 90% of middle-aged men can be simultaneously described as both 'active' and 'not sufficiently active' according to current physical activity recommendations (Thompson *et al.* 2009). As shown in Fig. 4, some people with very high physical activity energy expenditure will be labelled as not sufficiently active (and vice versa). Part of the explanation for this finding comes down to semantics but, in a recent study, we demonstrate that at least some of the problem comes down to the inherent heterogeneity in a given individual's physical activity (Thompson & Batterham, 2013). In this paper we proposed that novel approaches to capture (rather than ignore) the different physiologically important dimensions of physical activity are needed.

Implications for future research

Human physiologists are missing an opportunity to make more sense of their findings and to help move the field forwards. There are numerous reasons why physiologists should be looking to integrate measures of physical activity alongside other routine measures. These include (1) to characterise their participants in order to better understand their 'subjects', (2) to quantify any inter-individual variation in habitual physical activity energy expenditure

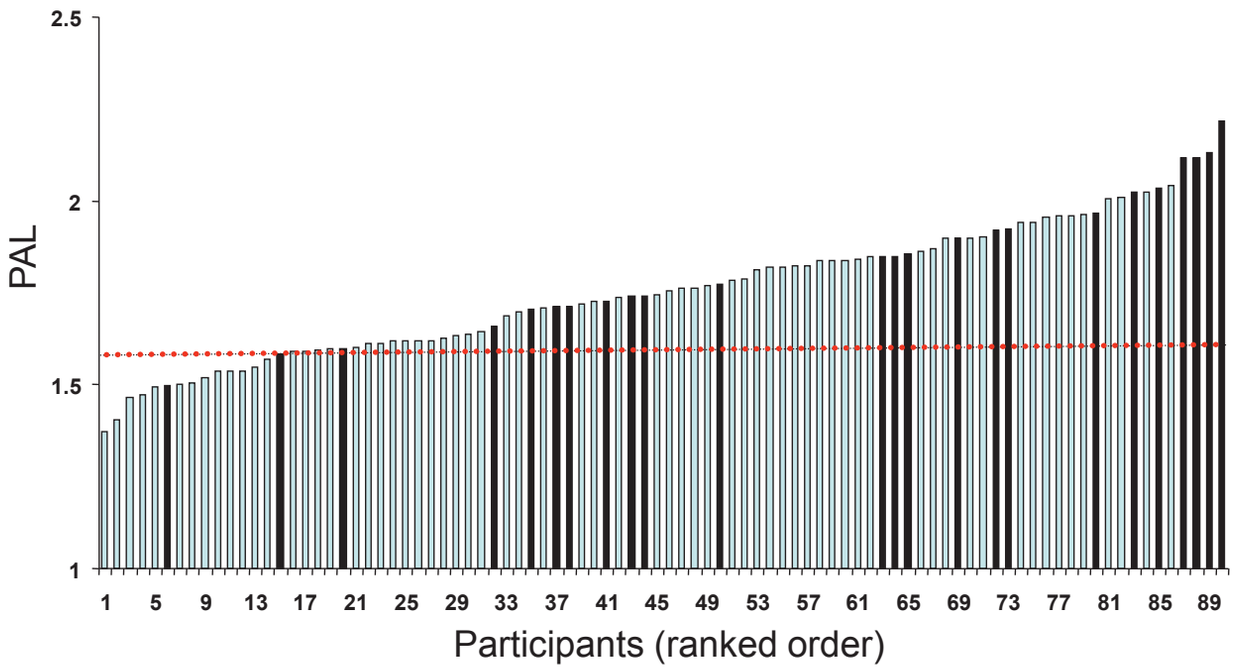

Figure 4. Ranked physical activity energy expenditure (PAL) for 90 middle-aged men (Thompson *et al.* 2009). The red line shows a PAL threshold of 1.6: this is sometimes used to determine whether physical activity is appropriate from a health perspective. The individuals with shaded columns also met the current recommendation from the American College of Sports Medicine/American Heart Association (i.e. 30 min of moderate intensity activity on at least 5 days a week in bouts of 10 min or 20 min of vigorous intensity activity on at least 3 days in bouts of 10 min).

in order to understand whether this accounts for variation in a given physiological outcome, (3) to determine the net impact of exercise interventions and the extent with which it supplements other physical activity energy expenditure, i.e. after taking into account factors such as substitution and compensation, (4) to facilitate better comparison between published studies in different laboratories and populations, and (5) to help work towards a resolution of the problems that are inherent in current public health guidelines for physical activity.

Conclusions

Physiologists have been slow to embrace the opportunities afforded by technological innovation in the capture of free-living physical activity energy expenditure. Instead, this has been left to epidemiologists and people working in public health. Physiologists have a unique role to play and it is time to recognise that being interested in measures of physical activity does not soften the science – it just makes the science better.

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The sympathetic nervous system and control of resting blood flow in adults with metabolic syndrome

The health consequences of obesity are well known: high blood pressure, high blood glucose and high cholesterol. But alongside these, other sinister effects may be going unmeasured. Does obesity affect the autonomic nervous system? And might a better understanding help us to manage health outcomes?

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Obesity epidemic

Over 35% of American adults are obese (Odgden, 2012). Obesity and obesity-related disorders, such as metabolic syndrome, are linked with increased cardiovascular disease risk, the development of type 2 diabetes, and increased all-cause mortality (Carroll & Dudfield, 2004; Ford *et al.* 2008). Thus, it is not surprising the American Medical Association recently adopted a policy recognizing obesity as a disease (AMA, 2013).

Metabolic syndrome is a condition in which adults are obese, have moderate-to-high blood pressure, high blood glucose, and high cholesterol levels (Ford *et al.* 2008). Each of these risk factors alone can contribute to adverse health outcomes; however, the clustering of risk factors within an individual increases a person's risk of developing cardiovascular disease above and beyond each individual factor (Carroll & Dudfield, 2004). In addition to measurable clinical markers (i.e. cholesterol, blood pressure, blood glucose), there are likely to be a number of subclinical adaptations that occur in adults with metabolic syndrome (Carroll & Dudfield, 2004). These potential markers of disease, by definition, go unmeasured during standard medical testing yet are likely to contribute to development of cardiovascular disease and type 2 diabetes in adults with metabolic syndrome. One possible subclinical change includes increased activity of the sympathetic nervous system. Consistent with this idea, elevated sympathetic nerve activity (SNA) has been linked to increased rates of cardiovascular morbidity and mortality and SNA is known to be increased in adults with metabolic syndrome (Lambert *et al.* 2010).

The sympathetic nervous system

The autonomic nervous system is divided into parasympathetic and sympathetic branches. The sympathetic nervous system, often described as the 'fight or flight' nervous system, plays an important role in the body's response to stress. For example, the anticipatory response to exercise (seen as a rise in heart rate, blood pressure and skin blood flow) is a result of changes in autonomic nervous system activity, including a rise in activity of the sympathetic nervous system.

Activity of the sympathetic nervous system can be measured in a variety of ways, with each method having its own inherent limitations (Mitchell & Victor, 1996; Wallin & Charkoudian, 2007). Microneurography, a technique first described in the late 1960s (Vallbo *et al.* 2004), allows researchers to safely record sympathetic nerve impulses in awake humans by placing a small, sterile wire microelectrode through the skin into a peripheral nerve carrying sympathetic nerve fibres. Microneurography allows for real-time and direct measurement of SNA headed toward blood vessels in skin and skeletal muscle. Activity of the sympathetic nervous system is identified in the form of sympathetic 'bursts' of action potentials (Fig. 1). An increase in the number and/or size of the sympathetic bursts in an SNA recording is associated with increased catecholamine (noradrenaline) release from sympathetic nerve terminals (Wallin *et al.* 1992, 1996).

Our research primarily focuses on the control of blood flow and blood pressure during physiological stressors such as exercise. Because blood vessels within the skeletal muscle play an important role in determining

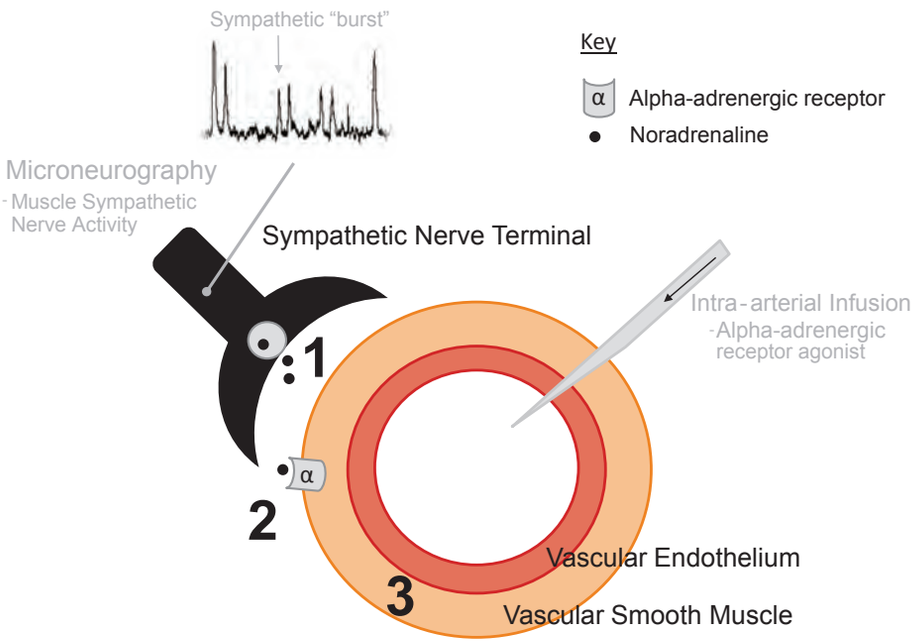

Figure 1. The sympathetic nervous system and control of resting blood flow. Activity of the sympathetic nervous system is identified in the form of sympathetic 'bursts' of action potentials which can be measured using a technique known as microneurography. An acute increase in the number of sympathetic 'bursts' will trigger increased neurotransmitter (noradrenaline) release from the sympathetic nerve terminals (Step 1). Neurotransmitters then bind onto their respective receptors (alpha-adrenergic) on the vascular smooth muscle (Step 2). Receptor binding initiates intracellular signalling that results in vascular smooth muscle contraction and vasoconstriction (Step 3). Thus, increased MSNA may result in a reduction in blood flow and increase in blood pressure. Figure adapted from Halliwill (2001).

total peripheral resistance and therefore blood pressure, we will focus our discussion on SNA directed to the skeletal muscle vasculature (muscle SNA, MSNA) and how changes in MSNA regulate blood flow and blood pressure.

Figure 1 shows how an acute increase in MSNA can reduce blood vessel diameter (vasoconstriction) and decrease the amount of blood flow delivered to skeletal muscle. In Step 1 MSNA triggers neurotransmitter release from the sympathetic nerve terminals (e.g. noradrenaline, ATP, neuropeptide Y). In Step 2 neurotransmitters bind to their respective receptors (e.g. adrenergic, purinergic, etc.) on the vascular smooth muscle. In Step 3 receptor binding initiates intracellular signalling that results in vascular smooth muscle contraction and vasoconstriction.

Over time, sustained elevations in MSNA can alter vascular responsiveness to neurotransmitters and cause structural changes in the blood vessels. If these changes cannot be offset by local vasodilatory factors, elevated MSNA may result in a sustained reduction in local blood flow and a rise in arterial blood pressure.

Transient increases in MSNA occur in response to physiological stressors such as mental stress, large-muscle mass exercises, hypotension (low blood pressure), and hypoxia (low oxygen levels). Sustained increases in MSNA are seen with hypertension, obesity, metabolic syndrome, heart failure and sleep apnoea, and are strongly associated with increased mortality risk (Wallin & Charkoudian, 2007; Lambert *et al.* 2010). Chronic sympathoexcitation is a possible therapeutic target for reducing blood pressure and mortality risk in these disease states (Hering *et al.* 2012; Paton *et al.* 2013)

Sympathetic control of the circulation: a balancing act

The exact mechanisms behind chronically elevated resting MSNA are unknown; however, chronic increases in basal MSNA occur in response to advancing age, increases in body fat, systemic inflammation, exposure to sustained or intermittent hypoxia (low oxygen), and altered insulin signalling (Scherrer & Sartori, 1997; Rumantir *et al.* 1999; Esler & Eikelis, 2006; Esler *et al.* 2006; Smith & Minson, 2012). With this information in mind, it may be surprising young, healthy adults with normal blood pressures exhibit a wide range of resting MSNA levels (e.g. 5–50 bursts min^{-1}) (Sundlof & Wallin, 1978; Narkiewicz *et al.* 2005; Wallin, 2007). Thus, rather than the amount of sympathetic activity (MSNA), it may be the integrated response to sympathoexcitation that determines how much vasoconstriction occurs, how much blood flow is reduced, how high blood pressure becomes, and ultimately whether or not increased MSNA contributes to cardiovascular disease.

Interestingly, in young healthy adults, chronic high levels of MSNA are not always associated with increased blood pressure and the development of chronic hypertension (Fig. 2A). This is likely to be the result of a number of checks and balances. Specifically, young men exhibit an inverse linear relationship between MSNA and alpha-adrenergic receptor responsiveness (Charkoudian *et al.* 2006; Hart *et al.* 2009, 2012). This means that the blood vessels in young, healthy adults with high basal levels of MSNA do not constrict as much to a given sympathetic 'signal' (e.g. MSNA, noradrenaline) when compared to healthy adults with low levels of MSNA (Fig. 2B). This inverse linear relationship may result from adrenergic receptor desensitization and/or downregulation (Steps 2 and 3, Fig. 1) in response to chronic increases in MSNA. Relative to everyday life, this phenomenon might be compared to olfactory fatigue – where prolonged exposure to a particular smell can lead to a temporary inability to perceive the smell.

Sympathetic control of the circulation in disease

Obesity-related disorders such as metabolic syndrome are sometimes referred to as 'early vascular ageing' because they tend to exhibit similar vascular outcomes to those seen in older adults, including chronically increased MSNA, vascular stiffness, and increased blood pressure. Although MSNA is known to be increased with age, not all older adults have high blood pressure. This may be due to the fact that, similarly to younger adults, older adults exhibit reduced adrenergic receptor responsiveness at rest (Davy *et al.* 1998; Dinenno *et al.* 2002) – indicative of receptor desensitization and/or downregulation.

Although research is limited in humans with metabolic syndrome, animal models of metabolic syndrome (often achieved using models of over-feeding and under-exercising) demonstrate increased sympathetically mediated vasoconstriction (Stepp & Frisbee, 2002; Naik *et al.* 2008). High MSNA that is

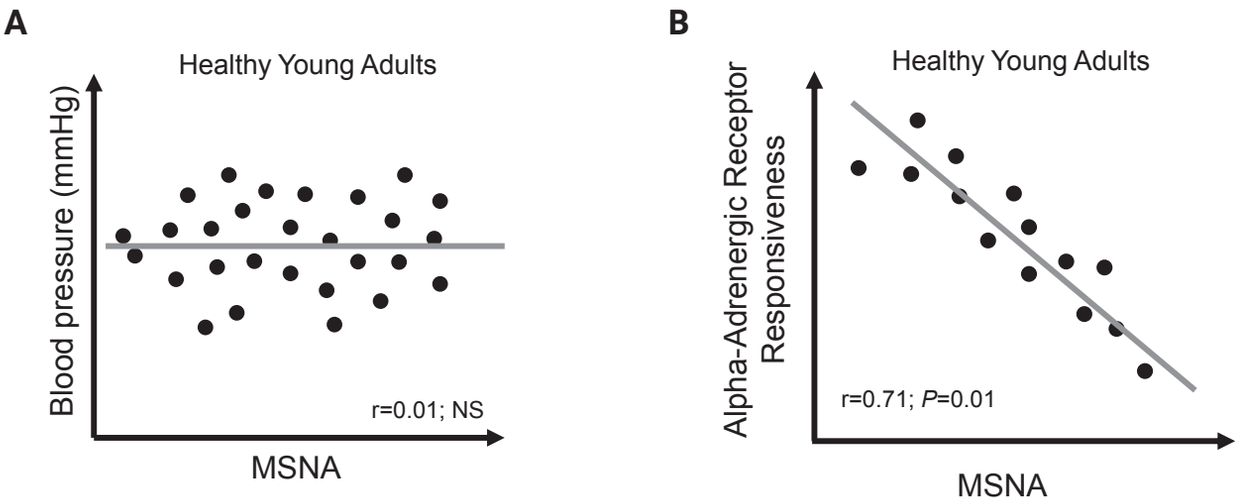

Figure 2. Sympathetic control of the circulation in health: a balancing act. A, in young healthy adults, chronic high levels of MSNA are not always associated with increased blood pressure. Figure adapted from Hart *et al.* (2012). B, healthy young men exhibit an inverse linear relationship between MSNA and alpha-adrenergic receptor responsiveness. This means that the blood vessels in young, healthy adults with high basal levels of MSNA do not constrict as much to a given sympathetic 'signal' (e.g. noradrenaline) when compared to healthy adults with low levels of MSNA. Figure adapted from Charkoudian *et al.* (2006) and Hart *et al.* (2009).

For simplicity, figure axes do not have numerical values as these vary between different source papers (see reference list).

not counteracted by reduced alpha-adrenergic receptor-mediated vasoconstriction (i.e. the inverse relationship between MSNA and alpha-adrenergic receptor responsiveness seen in healthy adults; Fig. 2B), may be an important factor in the progression of metabolic syndrome toward cardiovascular disease and type 2 diabetes. More specifically, high MSNA combined with high alpha-adrenergic receptor responsiveness in adults with metabolic syndrome could lead to constricted blood vessels, increased blood pressure, and less blood flow, oxygen and glucose delivery to the skeletal muscles.

Hypothesis, experimental design and results

Previous research from animal models of metabolic syndrome suggest several mechanisms by which blood pressure and blood flow control may be altered. However, potential species differences (rat vs. human) limit our ability to translate research directly from animal models to humans. To address this gap in knowledge, we measured basal MSNA and forearm blood flow in adults with metabolic syndrome and healthy control subjects (Limberg *et al.* 2012). Based on animal models (Stepp & Frisbee, 2002; Naik *et al.* 2008), we hypothesized adults with metabolic syndrome would exhibit greater alpha-adrenergic mediated vasoconstriction when compared with healthy adults. In addition, we hypothesized the inverse relationship between alpha-adrenergic responsiveness and MSNA observed in healthy subjects (a sign of adrenergic receptor desensitization and/or downregulation) would be lost in adults with metabolic syndrome. Because age can impact sympathetic control of blood flow and blood pressure (Hart *et al.* 2012), we studied relatively young (mean age 32 years) healthy and metabolic syndrome adults to focus on metabolic syndrome per se independent of any ageing influences.

First we used the microneurography technique described above to measure resting levels of MSNA. Confirming previous findings (Lambert *et al.* 2010), we observed higher levels of MSNA during quiet rest in adults with metabolic syndrome when compared with healthy controls (Fig. 3A). Second, to examine whether alpha-adrenergic receptors in adults with metabolic syndrome were more sensitive to a 'signal' to vasoconstrict (Steps 2 and 3), we placed a catheter (flexible plastic tube) into the brachial artery and infused an alpha-adrenergic agonist into the artery (Fig. 1). The selected agonist (phenylephrine) is designed to bind onto alpha-adrenergic receptors on the smooth muscle and cause vasoconstriction, which mimics the action of sympathetic neurotransmitters (Fig. 1, Step 1). This approach allows us to infuse the same concentration of agonist between adults with metabolic syndrome and healthy controls. A greater reduction in blood flow after infusion of phenylephrine indicates greater vasoconstrictor responsiveness. Adults with metabolic syndrome reduced blood flow in the forearm to a greater extent when compared with controls, which indicates adults with metabolic syndrome have greater alpha-adrenergic receptor responsiveness (Fig. 3B). Two key observations were made when we plotted each individual subject's MSNA (*x*-axis) and level of alpha-adrenergic responsiveness (*y*-axis). First, we confirmed previous findings from healthy adults (Figs 2A and 4A). Second, the inverse relationship between alpha-adrenergic vasoconstriction and MSNA is lost in adults with metabolic syndrome (Fig. 4B); this was previously unknown.

Taken together, MSNA and alpha-adrenergic receptor responsiveness is increased in adults with metabolic syndrome when compared with healthy adults (Limberg *et al.* 2012). In addition, high levels of MSNA in adults with metabolic syndrome are not counteracted by a reduction in alpha-adrenergic mediated vasoconstriction (Limberg *et al.* 2012). Thus, unlike young adults, the blood vessels in the resting skeletal muscle of adults with metabolic syndrome do not retain the ability to balance increased MSNA with decreased vasoconstriction. Without this important adaptation, adults with metabolic syndrome are likely to be unable to limit the impact of increased MSNA on systemic vasoconstriction. Consequently, adults with metabolic syndrome may be at a higher risk of impairments in blood flow, glucose disposal to the skeletal muscles, and regulation of blood pressure. Such impairments may promote the progression from metabolic syndrome to type 2 diabetes and overt cardiovascular disease. These results highlight early, pre-clinical changes in relatively young adults with

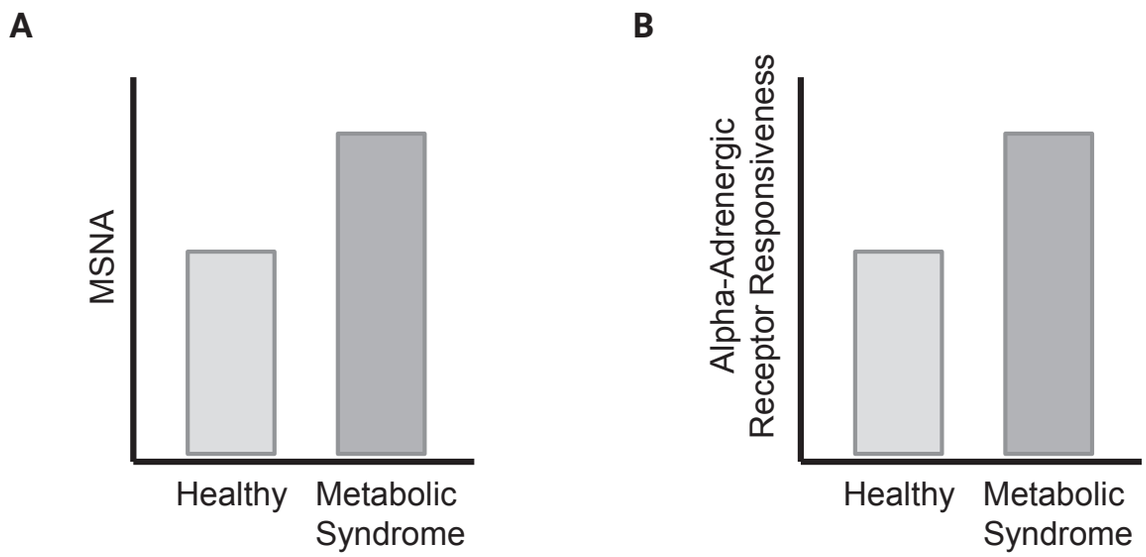

Figure 3. Sympathetic control of the circulation in metabolic syndrome. A, confirming previous findings, healthy adults exhibit an inverse linear relationship between MSNA and alpha-adrenergic receptor responsiveness. B, this relationship is lost in adults with metabolic syndrome. Figure adapted from Limberg *et al.* (2012).

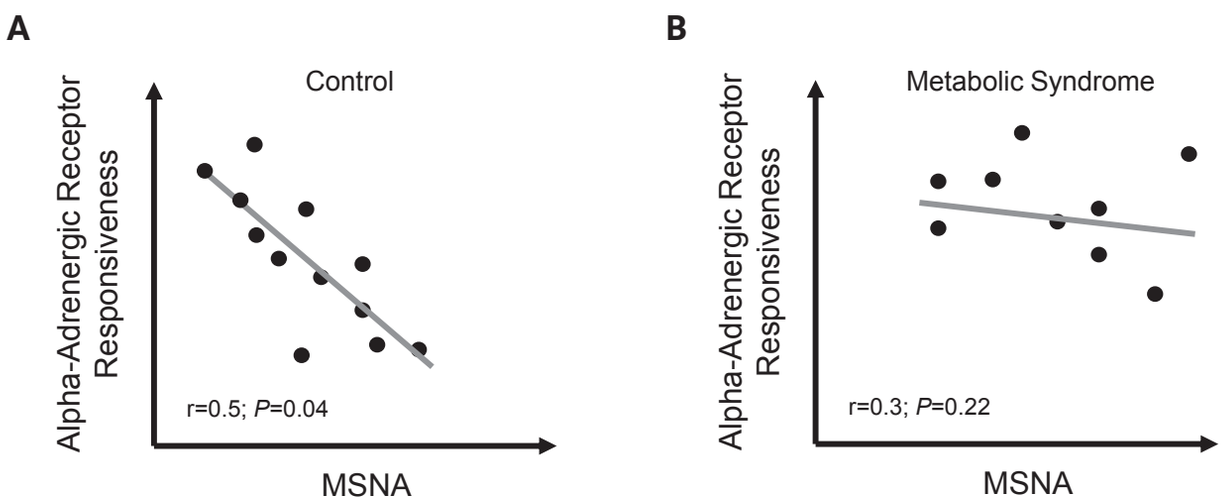

Figure 4. Sympathetic control of the circulation in metabolic syndrome. A, MSNA during quiet rest in adults with metabolic syndrome is increased when compared with healthy controls. Figure adapted from Limberg *et al.* (2012). B, adults with metabolic syndrome exhibit greater alpha-adrenergic receptor responsiveness when compared with healthy controls. Figure adapted from Limberg *et al.* (2012).

metabolic syndrome that likely contribute to increased cardiovascular disease risk.

The big picture

Over one-third of the population of the United States is obese and at increased risk of developing cardiovascular disease (Odgden, 2012). However, the transition from health to heart failure does not occur overnight. More often, a healthy adult with a normal body composition gradually becomes overweight, then obese, and then develops metabolic syndrome and type 2 diabetes, all prior to the onset of overt cardiovascular disease. Our recent findings (Limberg *et al.* 2012) add one more clue to understanding the progression from health to disease as it relates to sympathetic control of the circulation. First, alpha-adrenergic mediated vasoconstriction is relatively 'normal' in otherwise healthy obese adults (Agapitov *et al.* 2008). Second, alpha-adrenergic receptors fail to downregulate in a dog model of metabolic syndrome (Dincer *et al.* 2006). Third, MSNA and alpha-adrenergic responsiveness are increased in human metabolic syndrome (Fig. 3), suggesting alpha-adrenergic receptors fail to downregulate (Fig. 4B). Fourth, alpha-adrenergic mediated vasoconstriction is increased in adults with type 2 diabetes (Hogikyan *et al.* 1999). Taken together, younger adult humans with metabolic syndrome express an intermediate form of altered sympathetic regulation which may contribute to the development of type 2 diabetes.

Future research

Our study (Limberg *et al.* 2012) was performed under very controlled conditions;

thus there are still many questions to pursue in this research area. First, do all vascular beds adapt the same (e.g. forearm vs. leg vs. heart)? Second, do the sympathetic nerves release the same amount of neurotransmitter (noradrenaline) in adults with metabolic syndrome when compared with healthy adults? Third, do the number of alpha-adrenergic receptors change (e.g. downregulation) as a person develops metabolic syndrome or do signalling pathways within the vascular smooth muscle change? Fourth, are there systemic (e.g. cardiac output) or local (e.g. signals from the vascular endothelium) changes that could help blunt the effects of higher MSNA and possibly delay disease progression in adults with metabolic syndrome? Fifth, is the level of increased MSNA more or less important than the duration (e.g. years) of the disease? Clearly, there are several research questions which remain unanswered and many future directions to be explored.

Conclusion

Considering metabolic syndrome subjects were relatively young and free of overt cardiovascular disease, increased alpha-mediated vasoconstriction may contribute to reduced whole-limb blood flow, altered blood flow distribution, and severe hypertension as the disease progresses. Our recent study combined multiple physiological measures to fill a small, but important gap in our understanding of sympathetic control from health to disease. This approach uncovered some of the earliest subclinical changes in the progression from obesity to metabolic syndrome and type 2 diabetes, and emphasizes the complexity of sympathetic mechanisms of blood flow control.

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Optogenetics: An update

The new techniques under the label of optogenetics are illuminating brain structure and function. But what actually is it? How is it used? And how far has it taken us?

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Perhaps no other technology introduced into experimental bio-medicine has ever attracted such a surge of publicity than what is now commonly referred to as 'optogenetics'. A number of very good reviews on this topic are available and the key facts on molecular and engineering aspects can be found there (Chow *et al.* 2012; Carter & de Lecea, 2011; Lin, 2011; Mattis *et al.* 2012). This update is for those who are either considering or only just beginning to use it. It attempts to focus on the key features and history of this technology and share some thoughts on several issues which tend to receive less attention but which are nevertheless important.

In essence, the term 'optogenetics' only means a combination of genetic engineering and optical methods. From this perspective this technology can be traced back to the first experiments which applied green fluorescent protein (GFP) or even earlier. Today, two rather distinct families of protein tools are generally included in the term 'optogenetics'.

The first family comprises numerous fluorescent genetic constructs which are used as reporters or markers. In the simplest scenario they are used to visualise cells of interest, for example specific sub-sets of neurones in the brain, by inducing them to express a fluorescent protein, such as GFP. As we now have so many variants derived from several species with various spectra of excitation and emission, it is possible to combine proteins of different colours and in this way analyse the structure of the brain. This has been used to create the striking 'brainbow' effect where simultaneous expression of several differently coloured proteins generates distinct fluorescence hues in adjacent cells, thus facilitating structural analysis of the brain (Livet *et al.* 2007; Cai *et al.* 2013). Modifications of fluorescent proteins (mainly of GFP) are also used as indicators of intracellular signalling or trafficking processes. For example, a fluorescent marker protein can be fused to another protein which migrates from cytoplasm to the nucleus upon activation (so called translocation assays). Or, reporter tools combine fluorescent proteins in such a way that the construct changes its fluorescence upon binding with an intracellular second messenger (for example Ca^{2+}) or reacts to another signalling event, for example depolarisation of the membrane potential of a neurone.

It is, however, the second family, the optogenetic 'actuators' or 'effectors', which were introduced more recently and led to an avalanche of high profile publications. These constructs are derived from proteins which have conferred survival advantages to various simple organisms by allowing them to detect light. Our eyes contain an example of such a protein, rhodopsin, a G-protein-coupled molecule which acts as a photo-transducer. In fact, mammals express several rhodopsin-like molecules and whilst their function in the rods of retina is obvious, the closely related encephalopsins are found in the brain where their role remains a mystery (Blackshaw & Snyder, 1999).

Expressing light-sensitive proteins which can alter cell function in otherwise light-insensitive tissue such as brain or heart offers a remarkable opportunity for inducing changes to the activity of the targeted cells in a non-invasive way. Perhaps the first demonstration that this was actually possible was the study of Zemelman *et al.* (2002), which used a complex multi-component system of proteins that were co-expressed and used to control neuronal circuits in

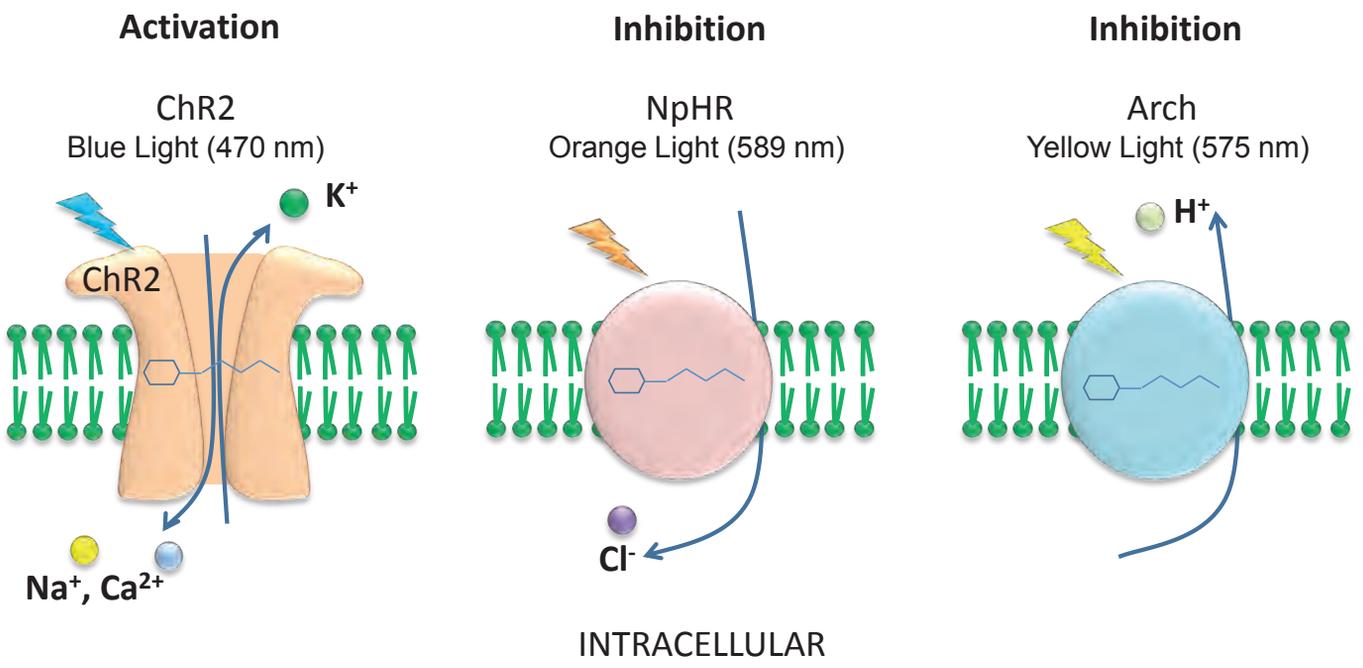

Figure 1. Three major classes of 'fast' optogenetic actuators.

Drosophila. In that system the signal from the trigger (light) was converted into an intracellular signalling event via G-proteins, which is the natural coupling mechanism for mammalian rhodopsins. While these experiments demonstrated the principle, the system was too complex to be easily adapted to mammalian cells and in addition too slow to allow what was deemed essential – a high degree of temporal control over neuronal action potentials with individual flashes of light.

The breakthrough came with the introduction of channelrhodopsin-2 (ChR2), a protein from the green alga *Chlamydomonas reinhardtii* (Nagel *et al.* 2003). ChR2, albeit structurally reminiscent of G-protein coupled receptors (it also has 7 transmembrane domains), works in an entirely different manner. Upon illumination it opens a non-selective cation pore permeable to Na^+, K^+, H^+ and to some extent to Ca^{2+}. In the membrane of a neurone such a conductance leads to a rapid influx of Na^+ and depolarisation that, if sufficiently strong, triggers action potentials (Fig. 1). At the same time, at neutral pH, the high H^+ permeability of ChR2 is of no significance because there is little drive for protons to move in or out of the cell. Very soon ChR2 was demonstrated to allow efficient control of activity in mammalian neurones (Boyden *et al.* 2005; Nagel *et al.* 2005). It came as a surprise that ChR2 did not even require supplementation with all-trans retinal, the obligatory co-factor for opsins, evidently because nervous tissue contains enough retinal which is also present in many culturing media (Boyden *et al.* 2005). Numerous mutants of ChR2 were then generated with the primary aim to increase channel conductance and speed up channel opening and closing in order to achieve more precise control of neuronal activity (Mattis *et al.* 2012). Optogenetic silencers (H^+ and Cl^- pumps) were also developed; see Fig 1 (Gradinaru *et al.* 2008; Chow *et al.* 2010).

Increasing conductance is important because in comparison with the native voltage-gated Na^+ channels which control action potentials, ChR2 conductance is low and it only works well when expressed at high density. A high level of protein expression can be achieved using powerful genetic targeting systems available today, but this also represents a challenge for the protein-producing and protein-sorting machinery of the cell, which may fail to deliver the majority of the expressed optogenetic actuator to the plasma membrane. After all, ChR2 is a foreign protein to mammals. In addition, fluorescent proteins are usually fused to the actuators and this worsens the situation because these may fold imperfectly or form multimers. This may lead to ER stress and be damaging to the cell. If light-sensitive channels partially remain in the endomembranes, they might be activated upon illumination, possibly releasing Ca^{2+} stored in intracellular organelles. Whether such retained actuator molecules are functionally relevant and play a role in the effects of ChR2 is not known but should be investigated. Efforts are ongoing to improve maturation of optogenetic proteins and their targeting to the plasma membrane by targeted mutations and by integrating specific trafficking signals.

Adjusting kinetics of ChR2 and similar actuators is important for several reasons. First, faster depolarisations and repolarisations allow more accurate control of neurones with short flashes of light. For some slowly spiking neurones this is less crucial, as typically even the first generation of ChR2-like proteins successfully deliver firing rates of 20–30 Hz. However, for fast spiking cells, frequencies of up to 100 Hz may be desirable and here light-sensitive channels still have room for improvement, in spite of significant recent progress. Ideally one would want to illuminate with light pulses of a duration similar to naturally occurring action potentials (typically around 1 ms) in central neurones, but generating enough current with such short flashes is difficult and may require using high light intensities which may be phototoxic. Hence almost all published studies use light pulses of 5–20 ms or even longer. It is important to realise that the feasibility of driving high frequency bursts with ChR2-like proteins also depends on the type of cell which is to be stimulated. A large neurone would typically have a relatively low input resistance (e.g. significant leak of current across its plasma membrane) and a large membrane capacitance. Hence it is much harder to drive it faster than a small compact cell, which can be efficiently depolarised with relatively modest currents created by ChR2. In addition, comparatively slow ChR2 kinetics means that the membrane remains depolarised slightly longer than the end of the light pulse, thus permitting longer activation of voltage gated Ca^{2+} channels and stronger Ca^{2+} influx than during native action potential activity. As a result, neurotransmitter release caused by flashes of light applied to ChR2-expressing synaptic terminals could be stronger than if it was driven by physiological action potentials. The same applies to

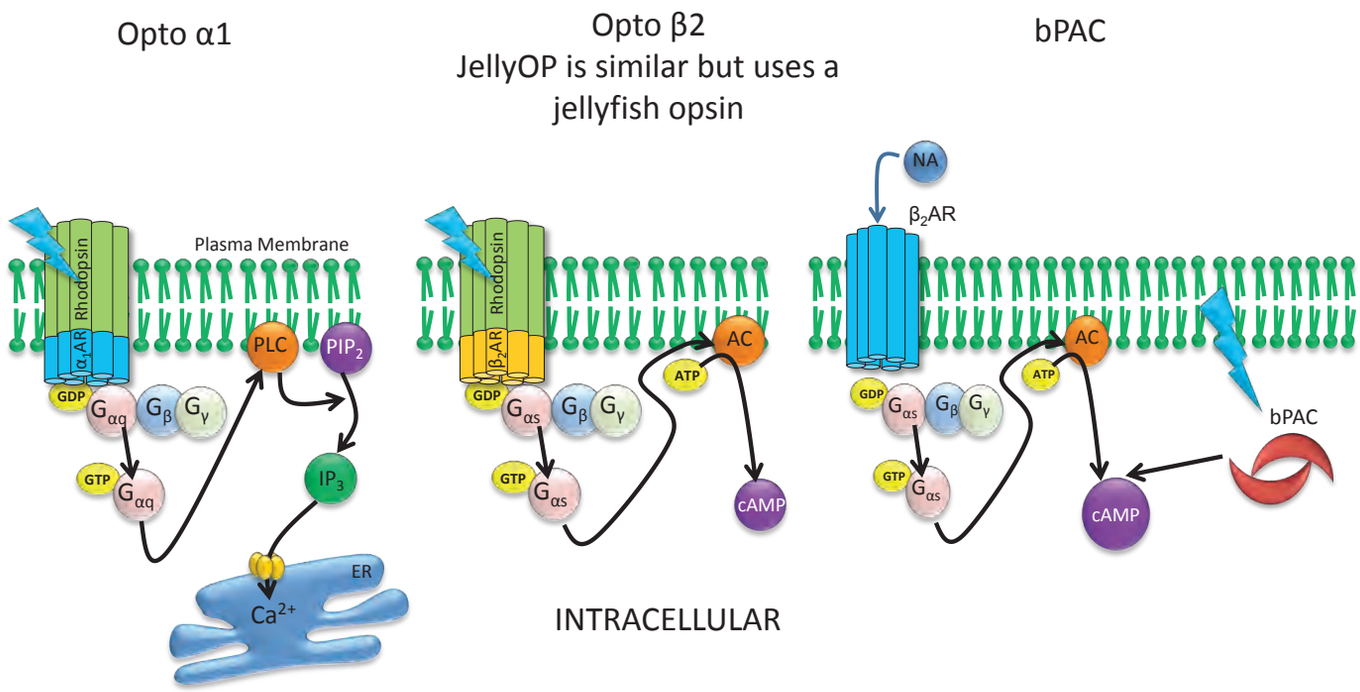

Figure 2. Optogenetic actuators can control intracellular signalling in a manner similar to G-protein coupled receptors.

somato-dendritic release of neurotransmitters when ChR2-expressing somata of neurones are stimulated with light. Powerful somato-dendritic release could have various functional consequences, for example triggering a negative feedback response – consider, for example, noradrenaline acting on α2-adrenoceptors which are coupled to Gi proteins. Overall, there is a fine balance between the speed of activation and inactivation of a light sensitive channel, its unitary conductance, density on the plasma membrane, sensitivity to light and the intrinsic electrical properties of the membrane of the neurone (or other cell type) to be stimulated (Mattis *et al.* 2012). The cycle of activation and inactivation of light sensitive cation channels can be varied and some mutants, once activated, remain in the open state for many minutes. This property has led to development of the so-called step-opsins (Berndt *et al.* 2009), which can be used when precise timing with pulsatile light is not essential but prolonged application of light is technically difficult.

A further useful development has been the variation of spectral characteristics of optogenetic actuators. ChR2 and its closest relatives are best activated by blue light, typically by 470 or 445 nm lasers or diodes. However, sometimes it may be desirable to use longer wavelengths for excitation. *In vivo* longer wavelengths travel further through the tissue thus helping to increase the effective volume of activated tissue. Most of the constructs used today are mutants of ChR2 or its chimeras with ChR1 from the same species and they all have excitation maxima below 500 nm. However, chimeras between ChR1 and VChR1, a light-sensitive channel from *Volvox carteri*, can be efficiently excited by green or even yellow light (~550 nm) (Mattis *et al.* 2012). The most spectacular development in this direction is the ReaChR, recently published by J. Y. Lin and R. Y. Tsien (Lin *et al.* 2013).

While numerous mutants of ChR2-like light sensitive channels have been generated, most of the focus has been on either improving their dynamics (faster vs. slower currents) or varying their spectral characteristics (e.g. excitation maxima). By contrast, one rather fundamental property, ion permeability, has received comparatively little attention. Engineering ion-selective versions of ChR2-like channels is, of course, not trivial but could result in some very useful improvements compared to a non-selective cation permeability. First of all, removing the concomitant K^+ conductance should make these channels more efficient depolarisers. Second, generating a selective light sensitive Ca^{2+} pore would be highly advantageous for many studies which focus on the role of Ca^{2+} but do not require membrane depolarisation (for example for control of non-neuronal cells). Here some efforts have been made (Kleinlogel *et al.* 2011) but clearly there is room for improvement. Finally, if it was possible to confer K^+ selectivity to a ChR2 pore, this would result in a highly efficient light-sensitive 'off-switch' for excitable cells. Moreover, theoretically it could be even converted into a step-function off-switch – a construct which once activated by a flash of light remains in that state for a significant length of time. The light sensitive ion pumps Arch and NpHR (Fig. 1) are currently available for this purpose but work on a slightly slower time scale and require constant illumination because they are energy dependent (Chow *et al.* 2012).

In addition to light-sensitive ion channels, two further classes of optogenetic actuators are increasingly coming into use and deserve mentioning (Fig 2). The first class are G-protein-coupled light-sensitive proteins, one example of which are the opto-adrenoceptors, chimeras of rhodopsin and adrenergic receptors with a choice of intracellular coupling mechanisms. Construction of such chimeras was possible because of the domain organisation of G-protein-coupled receptors, which permits switching of various components of these proteins (Kim *et al.* 2005; Airan *et al.* 2009). These tools cannot be used to control neuronal spiking with any temporal precision, but on the other hand they offer a very attractive way for exploring effects controlled via G-protein-mediated signalling cascades. Since the original publication in 2009, there have been no studies using these receptors, which may be suggestive of technical difficulties. A recent study described a new light-sensitive chimeric G-protein-coupled receptor, 'JellyOp', which uses parts of a bleach resistant opsin from *Carybdea rastonii*, the box jellyfish (Bailes *et al.* 2012). JellyOp couples to adenylate cyclase and promises to be a useful addition to the previously available toolbox.

The second class are the light sensitive enzymes, exemplified by the photoactivated adenylyl cyclase from *Beggiatoa* (Stierl *et al.* 2011). The interesting feature of this approach is that a short pulse of light is

sufficient to activate the enzyme, which then generates cAMP for some time and thus greatly reduces the risk of photo damage. The difficulty is to make such proteins completely inactive in the dark state, something yet to be achieved.

For obvious reasons the ability to selectively activate selected neuronal populations by light was most appealing to neuroscientists working to disentangle multiple and intermingled neuronal networks within the brain. However, the use of optogenetic actuators in neuroscience is not limited to triggering or inhibiting neuronal action potentials. In fact, optogenetics can be effectively used to study non-excitable parts of the brain supercomputer, the glia cells. When ChR2 is expressed in astrocytes, light flashes transiently depolarise astrocytes, as they would with neurones, but these depolarisations appears to have little immediate effect on astrocytes or adjacent neurones. However, optogenetic activation of astrocytes leads, with some delay, to the release of 'glio-transmitters' such as ATP and activation of astrocytic and connected neuronal networks. Given that there is currently no other non-genetic way to selectively activate astrocytes, this imperfect tool can nevertheless be very effective (Gourine *et al.* 2010; Figueiredo *et al.* 2011). Opto-adrenoceptors and JellyOP mentioned above could be preferred tools for selective control of non-excitable cells where cellular physiology is often controlled by IP3 or cAMP concentrations. Control of cellular function by light is of course also applicable to tissues outside of the brain (Auslander & Fussenegger, 2012).

Finally, what is left to do for genetics in opto-genetics? In fact, the success of optical interrogation of brain function is critically dependent on the ability to selectively express optogenetic actuators and other molecular tools exclusively in the cells of interest. Two general strategies are currently being used for targeting. Either the experimentalist relies on the use of a viral vector with a cell-selective promoter (e.g. CamKII or GFAP promoters) to target expression of the actuator. Or, the selectivity is determined by transgenic expression of CRE recombinase while the optogenetic gene is delivered by a CRE-dependent viral vector or by breeding a CRE-driver mouse into another strain which contains the construct which needs to be switched on by CRE. Numerous CRE-deriver mice are available and many have very tightly controlled cellular specificity. However, for many types of experiments, the rat remains a better option, and the choice of CRE-driver rats is extremely limited. Achieving a high degree of specificity with short promoters that are suitable for viral vector-mediated expression is difficult and unfortunately only a few such promoters are yet available, but where they are available, this approach offers great flexibility and speed. The downsides are some risk of tissue reactions to viral particles and the fairly small choice of potent and selective promoters, which are very hard to design rationally. Still, we believe that many more cell-selective viral targeting systems can and should be generated. Altogether, improvements in the gene expression systems are essential for future progress in application of optical tools.

In summary, optogenetics has now reached the stage where it has become a recognised and widely used technology in physiology. There are many improvements which can and should be made to the existing tools and their means of delivery. We look forward to further developments in the near future.

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Q&A: Gero Miesenböck

Optogenetics allows genetically specified populations of neurons to be turned on or off with light. *PN* talks to the leading developer of the technique to explore the inspiration and drive behind creating one of the most powerful tools to open up a whole new region of neurobiology, and the quest to discover how the brain makes informed decisions.

Gero Miesenböck

Waynflete Professor of Physiology, University of Oxford

Director, Centre for Neural Circuits and Behaviour

What led you to physiology?

I had a circuitous route into physiology. I studied medicine in Austria – where I'm from – but discovered early on that clinical medicine and I were not made for each other. I liked the basic science subjects but got bored in the clinic. I also realised that being able to repeat a failed experiment is a good thing. So I did research as a medical student on lipoprotein metabolism, came across Goldstein and Brown's work on receptor-mediated endocytosis and became fascinated by cellular membrane trafficking. This led me to do a post-doc with Jim Rothman, who was just today announced as a winner of this year's Nobel Prize in Physiology or Medicine. I initially worked on a cell biological problem in his lab but later began to develop genetically encoded optical reporters for imaging synaptic transmission. The combination of genetics and optics has been a recurring methodological theme ever since.

What inspired you to create optogenetics?

I had worked on genetically encoded fluorescent proteins and engineered them to make neuronal activity visible. Optogenetics, as it's now understood in its narrow sense, is communication in the opposite direction: you don't make neuronal activity visible, you use light to elicit or suppress it.

I was steeped in thinking about optically active proteins and neurons but wasn't actively trying to invent optogenetic control when I had the idea. It was a Saturday, I was at home and drifting back into a novel I was reading, and suddenly I thought, 'Wouldn't it be amazing if one could invert the direction of optical communication with the brain. Use light not just to observe, but also to control.' As soon as I had the idea I realised that if it worked it would have a major impact.

It was a high risk thing; it was by no means clear that it would work. There were many improvements that came after our initial proof-of-concept experiments, and these improvements contributed to the rapid spread of the technique. Needless to say not all of the improvements are ours – a few people have made important contributions. It's been more than 10 years since we reported the fundamental concept of optogenetic control: the idea of putting a photoreceptor like rhodopsin into a neuron in order to control its activity with light. Like all these things, it started slowly with just my lab. In 2005 we showed we could remote-control the behaviour of an animal – that was another milestone that began to capture people's imagination. A few months later channelrhodopsin was substituted for the rhodopsin we had initially used. This improvement made the whole approach much simpler to use, and the field exploded.

What is it like to lead a team whose work is receiving so much attention?

You don't think about the attention of others when you try to solve a problem – it was never on the forefront of my mind. I'm captivated by the scientific question at hand. The driver behind all of it was curiosity about how the nervous system works rather than a desire to push methodologies. The biological problem still remains what I find the most stimulating.

What are the most important doors that optogenetics will continue to open within research?

Our very first paper ended with two short

paragraphs outlining what might become possible, *in vitro* and *in vivo*. These paragraphs contain, in a nutshell, an accurate prediction of how the field has developed. *In vitro*, you can take an explanted piece of brain tissue, such as a brain slice, and reconnect it to artificial inputs that have physiological relevance. You can literally talk to a piece of brain tissue in the controlled setting of a dish. This is something that just hadn't been possible as long as the senses were the only portals of communication with someone else's brain. Perhaps the most straightforward example of such an *in vitro* experiment is the mapping of functional connectivity by putting a listening post – be that a fluorescent dye or an electrode – into one cell and then probing around quickly with a laser beam to get a picture of which cells communicate with the target.

In vivo, the key approach that optogenetics has enabled is to pinpoint the neuronal substrates of behaviour more precisely and directly than before. Neuroscientists can finally perform reconstitution experiments – something that geneticists and biochemists have been able to do for a long time. You have to ask yourself what reconstitution would entail in neuroscience. You can't just take a brain, grind it up, purify the components and put them back together. But what reconstitution can be is taking pure activity patterns, playing them back to the intact nervous system and seeing whether you can elicit a specific behaviour. That's something that was possible only to a very limited extent before optogenetics, but that we can do now.

The other thing that optogenetics has allowed us to do is to skip all the peripheral processes. In the past, if you were a neurophysiologist you would usually go about probing the brain by showing an animal something on a screen, giving it something to smell or playing some tones for it to listen to. Your approach to the neural circuitry behind the senses was always indirect; the senses were the gatekeepers that would determine the kind of information you could feed into the brain, and you couldn't be sure what you were supplying. With optogenetics, you can jump right into the middle of a circuit, which I think has also been a great, great advance.

What do you think will be the most important therapeutic applications for optogenetics?

The most immediate and obvious area where optogenetics can probably help is visual restoration. If you have damage to or degeneration of your photoreceptors, you might restore light sensitivity to other neurons in the retina – this might bring back a significant amount of vision. I think the advantage of focusing on the retina first is that the problem of delivering a foreign gene and expressing a foreign protein is less acute because the eye is a privileged compartment both in terms of access and also immunologically. For this and all other applications of optogenetics, a genetic modification is a key requirement. So while our flies and other people's mice don't mind, I think most humans still do!

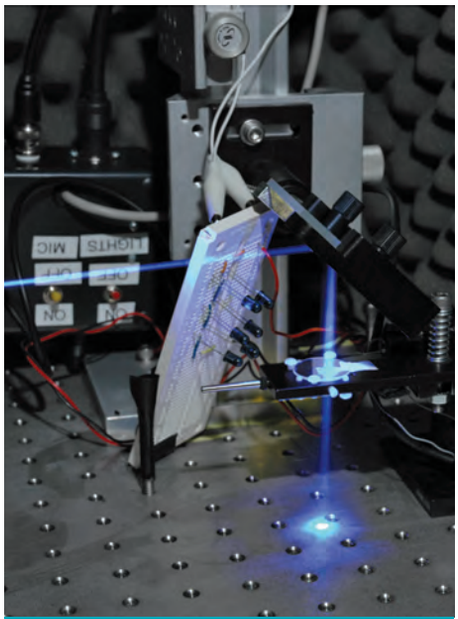
Do you think that there is a risk of the technique being abused?

I think the potential for abuse is there with many medical advances. There's often a narrow line between what's beneficial and what's potentially dangerous. That said, I don't think that things like mind control of people or the use of remote-controlled animals as weapons is something that's anywhere around the corner. We simply don't know enough about the basic neurobiology of the processes that would be involved. If we understood completely how, for instance, a fly navigates its environment, selects a target, hovers, and perhaps lands and takes off again, we would be very happy campers, but we don't know any of this. When our paper on optogenetically controlled flies appeared in 2005, an American journalist called and asked me: 'So when are we going to invade another country with an army of remote-controlled flies?' The answer was then, as it is now: 'Not any time soon.'

What are the next steps for optogenetics?

I think there is significant development that needs to happen on the optical side of things. In most experiments light is delivered by relatively simple means. You just either shine light onto an entire animal, as we do with our fruit flies, or you insert a fibreoptic cable into certain nuclei in the brain and illuminate these areas completely. But in many cases I think it would be really nice to be able to control the members of a population of neurons independently, and also to have some kind of direct read-out of what the individual nerve cells are actually doing. Are they obeying our optogenetic commands or just rolling their eyes and doing what they feel like, like sullen teenagers? To find out would be a huge technical challenge, one I don't even know how to begin to address. But if we could there's a whole range of basic science questions that would open up, including clever ways of feedback control.

Another area of great difficulty and promise is in the genetic targeting of cells. One of the key innovations of optogenetics is to use genetic address labels in order to single out specific neurons in the brain like needles in a haystack. But it turns out that most of the address labels we currently use are not sufficiently precise. Our addresses often consist only of the name of a town or county, when in reality we would like to direct our optical messages to individual houses in a town or specific inhabitants in a house. To develop a genetic postcode that would allow us to do this in a systematic fashion would be a real breakthrough.



Optogenetic activation of a fly's courtship song in a custom-built sound studio

What is the next big thing for you?

We are after the elementary logic of information processing in the brain. Although much of this work is done by studying particular behaviours in fruit flies, we don't care all that much about these behaviours or the fact that they occur in flies. Rather, our research is motivated by the belief that animals do not employ an endless variety of brain circuits, but a limited set: circuits that compare signals, apply thresholds, integrate information, keep time, store memories. We approach these circuits by studying particular behaviours in the fly, but the goal is always general – we just use these particular behaviours and this particular organism to get at things that we believe are fundamental to all brain function. Some of the circuits that we are especially interested in at the moment are those that keep track of events over longer time scales: circuits that can take information and not respond instantly like a reflex arc, but that actually hold and weigh and ponder the information over extended periods of time.

We also have some other techniques that we are developing, but these are of course still trade secrets!

Further information

Gero's talk on re-engineering the brain: www.ted.com/talks/gero_miesenboeck.html

Centre for Neural Circuits and Behaviour: www.cncb.ox.ac.uk

New members of Council

This year, eight Members were elected to The Society's governing Council. *PN* spoke to each of them to find out who they are and how they came to be playing such a crucial role for The Society.

Susan Deuchars

Reader in Neuroscience, University of Leeds

I work on spinal cord circuitry, looking at which neurones communicate to enable appropriate autonomic control, but also trying to see whether there are interneurons in the spinal cord which have a more global effect, trying to co-ordinate autonomic and motor output. I've never moved away from this area; I did my PhD in London with Mike Spyer and Mike Gilby, and I just kept working on it. There's so little known about it.

I've been a Member of The Society right from the beginning of my PhD, in 1988. Both my husband [James Deuchars] and I joined as Affiliate Members.

Everyone joined The Society in those days. Everyone who worked at the Royal Free Hospital was a Member. I just thought it was brilliant. I remember meeting people, Rob Clarke in particular, who was an absolute hero of mine since he was so friendly and helpful. He was a real stalwart of The Society.

I think PhySoc is really important. I consider myself a neuroscientist but I like the fact that you can't take the central nervous system away from the rest of the body. I think the PhySoc is an excellent forum for discussing new ideas and encouraging new scientists; the meetings are fantastic for allowing everybody to mingle. So many other meetings cost such a lot of money – PhySoc is still accessible to all. So I really wanted to get involved and maintain that.

I think Members have got to know me because I've been a Theme leader (Cardiac and Respiratory Theme) since 2004 and I organised one of the first Theme Meetings in Leeds in 2008. I am also always hassling people to do posters.

What I really liked about my first Council meeting is that it's still got that feeling of people belonging and caring about making PhySoc a Society for all physiologists, regardless of their level. I enjoyed the Meetings Committee too, they're a very enthusiastic crowd!

Sue Deuchars sits on the Meetings Committee

Anne King

Reader in Neuroscience and Director of the programme for Human Physiology, University of Leeds

I started off looking at motor outputs from spinal cord but then became more interested in sensory inputs, especially pain and nociceptive inputs. I am interested in translating an understanding of pain processing into clinical therapies for chronic pain. For example, there is a huge unmet clinical need for neuropathic pain.

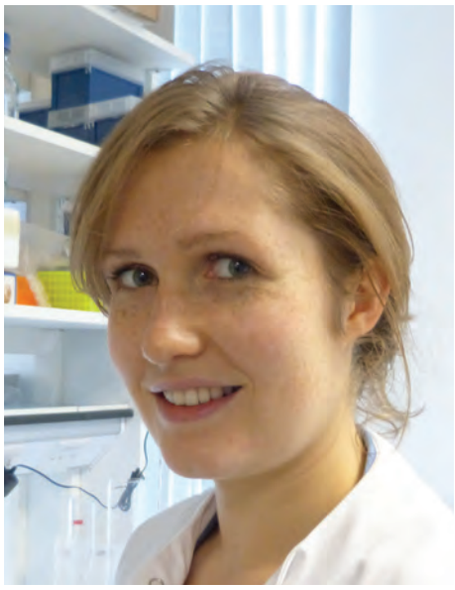
I joined The Society in 1987; I would have been a post-doctoral researcher at that time. I joined as soon as I possibly could because I wanted to be part of the UK Physiology community and the best way to do that was to become a member. The criteria for membership were rather strict in those days – much tougher than now!

I first came onto Council in the mid 1990s. I sat at different times on the Education Committee, the International Committee and then I chaired the Grants Committee. Recently I got drawn back in and I'm now the Honorary Treasurer! But even when I was not a member of Council, I was still very much involved in The Society in one way or another.

I think there is an under-representation of women in science, especially at senior levels and on national committees that have influence. But if there's not enough representation, perhaps it's because not enough women are putting themselves forward. So then, you think, well, I should do that myself instead of leaving it to others.

When the opportunity came to contribute to The Society's activities in a way that was new for me, that was attractive. I've had to learn quickly a lot about what it means to be the Honorary Treasurer but it has been interesting too. As Honorary Treasurer, I can work to support the membership and its activities. I think Physiology is under threat in terms of its perceived relevance to society. It's obvious to us why it is so important, but it's not necessarily obvious to a broader audience. So I like to support work in that area too.

Anne King is The Society's Honorary Treasurer and sits on the Executive Committee, Finance Committee (as chair), Publications Committee and History and Archives Committee.



Ruth Norman

PhD student, University of Leeds

My PhD project explores molecular changes that occur in heart disease, with a focus on beta adrenergic receptors and caveolar proteins, under the supervision of Sarah Calaghan and Ed White. I also teach anatomy to undergraduates.

I joined The Society just last year. Most people in my lab attend the conferences and say that they're a good opportunity. My post-doc, David MacDougall, said that it was really worthwhile joining, and there is another PhD student in my lab who actually came to Leeds because he met people in the Leeds group at a Society meeting.

This is the first active involvement I've had with The Society, though I presented a poster at the IUPS conference in July [hosted by PhySoc]. An international conference is pretty good going for starters! I'm lucky that it was hosted by PhySoc in the UK.

As an undergraduate I was the student representative for my course and I enjoyed that role, so I applied to be an affiliate representative on Council. I emailed Keith [Siew] and Jamie [McPhee – former affiliate representatives on Council] to ask how they found the role and they both said it was very rewarding being involved and promoting early-career scientists. I didn't know them – they were just given as contacts in The Society's email newsletter.

The first Council meeting was quite a lot to take on board. I didn't realise how much goes on behind the scenes and how much work was involved in running Society activities; how much you have to put in to give out benefits to Members.

Ruth Norman is an Affiliate Representative and sits on the Meetings Committee

Lucy Donaldson

Associate Professor, University of Nottingham

I research mechanisms of chronic pain and taste disturbances in disease states. I originally trained as a dentist. When I intercalated in neuroscience at the University of Edinburgh, I developed an interest in pain. Many thought it hilarious that a dentist was interested in pain, but it was from exposure to great teaching that my interest developed, rather than from anything I inflicted on a patient!

I became interested in taste disturbances much later on as a result of teaching dental students at Bristol University, and wine tastings with friend and psychiatrist, Jan Melichar.

I attended my first PhySoc meeting in London under the Young Physiologist Guest Scheme at the suggestion of my (now) husband [Dave Bates]. I first presented at a Bristol meeting, where I met many of the people with whom I now collaborate. Both meetings were in 1992.

I didn't actually join The Society until I moved to a faculty position in Bristol in 1999, when Bridget Lumb mentioned she was surprised I wasn't a Member. I immediately joined and became convenor for the Somatosensory SIG. When Society Reps were introduced, I fulfilled that role at Bristol and did so until I moved to Nottingham this summer. Being a rep was a really good way to get to know both The Society and the university – you find physiologists in the most unexpected places when you're a rep.

I stood for Council because I want to help make sure that physiology remains a vibrant community with strong representation at local, national and international levels.

Lucy Donaldson sits on the Policy Committee

Mike Ludwig

Professor of Neurophysiology, University of Edinburgh

I am Professor of Neurophysiology in the Centre for Integrative Physiology at The University of Edinburgh. My research interests focus on the basic mechanisms by which neuropeptides affect the functional properties of neuronal networks, and exactly how they can have apparently specific behavioural effects.

I obtained my PhD in neurobiology from the University of Leipzig, Germany, and pursued postdoctoral studies at Wake Forest University in Winston-Salem, North Carolina, USA. I came to Edinburgh in 1995 and my association with The Society began when I became an Associated Member in 1995 and a full Member in 1998.

I was convenor for the Special Interest Group 'Neuroendocrinology' for The Society from 2005 till 2009. Since 2009 I have been Theme Leader for Endocrinology and Metabolism.

Over the years I have regularly assessed symposium proposals and abstracts, chaired sessions and evaluated posters at meeting of The Society.

I have organised several symposia, including: a symposium entitled 'Dendritic neuropeptide release' at Life Science in Glasgow (2007); with Prof Alison Douglas a Physiological Society International Focus Meeting 'Perinatal physiology: from uterus to brain' in Edinburgh (2007); and a Special Physiological Society Symposium to honour the lifetime achievements of Professor John Russell (Festschrift) in Edinburgh (2009).

In 2013 I was elected as a Trustee to support The Society in this role.

Mike Ludwig sits on the Meetings Committee

Prem Kumar

Professor of Physiological Science, University of Birmingham

I've long been interested in the mechanisms of action and role of peripheral chemoreceptors. This interest, which now encompasses glucose sensing and obstructive sleep apnoea, in addition to hypoxic chemotransduction, arose from mentoring and teaching by Bob Torrance, Piers Nye and Mark Hanson, who all imparted their passion for the topic to me.

The interest is now retained by the stubborn refusal of the carotid body to reveal its secrets easily and also by the great friendships I have made over my career with others who share the same enthusiasm.

I gave my first oral presentation to The Society in 1983 (was that really 30 years ago?), and joined as a full Member in 1991 when I became a lecturer in a physiology department – where it was just a natural thing to do. I still recall the anxiety I felt when it was revealed that a single Society Member could effectively veto an application to join if they deemed you 'not worthy'! Luckily, I passed the test and those old 'dining society' rules have now been removed.

Since then, I have had the privilege of being the Meetings Secretary for The Society, helping to establish the annual meeting format and a greater international flavour to our UK Meetings.

I have re-joined Council to work with the Education and Outreach Committee where I feel we have a lot to do to keep physiology and our Society remaining vital to the next generation of life scientists in schools and universities.

Prem Kumar sits on the Education and Outreach Committee

Rachel Tribe

Reader In Women's Health, King's College London

My research focuses on the mechanisms controlling human parturition and reasons why women deliver their babies prematurely. My group aims to identify drugs that can stop premature labour when it happens, with a particular interest in potassium channel modulators that can target the uterus.

The Physiology Society Main Meeting was the first conference I ever went to – the meetings provided me with a fabulous opportunity to learn about many different systems. I didn't join The Society until 1996, after my first post-doc, when I was encouraged to do so by Lucilla Poston, Jeremy Ward and Sarah Hall, who were all Members at the time.

Since 1996, I have presented whenever I can at meetings and encouraged all my students and staff to join The Society as it provides tremendous networking opportunities as well as providing a close network community for scientists. This is really important to me, being embedded in a medical environment. I have over the years taken on ad hoc roles at Society meetings, such as poster judging and chairing sessions. Iain Greenwood persuaded to be co-convenor of the Smooth Muscle Interest Group [2007-2010], an experience which gave me the confidence to take on other roles.

I am glad to be involved more now as a Trustee and member of the Council. It is fascinating to understand how the Society functions, and to be able to be support the Society in this way. I am particularly looking forward to be being involved in more Outreach and Education activities.

Rachel Tribe sits on the Membership and Grants Committee and the Education and Outreach Committee

Fiona Hatch

Post-doc, University of Surrey

My post-doc is focused on the cardiac pathology atrial fibrillation (AF). My focus is to investigate the mismanagement of electrical activity during AF.

I joined The Society when I first started my PhD back in 2009 and was told that it would be worth being part of, if just for the travel grants. It was not until Physiology 2012 [Edinburgh] that I really saw the benefit of The Society. No longer was it about the funding, but the science, the networking, the experiences, and the mentoring and advice offered by senior physiologists.

In 2012, I entered and won the I'm a Scientist, Get Me Out of Here event, which I did because I feel that science should not be exclusively for scientists, but should engage the public. In Edinburgh I met the previous affiliate representative, Keith Siew, and through him I learnt more about what The Society was doing in this area. So, I decided to apply for Keith's position on Council when he stepped down. I am now also part of the Education and Outreach Committee, and the Policy Committee. Both I find important and enjoyable, and of real value to my personal development and career.

I am so thankful that I became a Member of The Society: the people you meet, the science you discover, the networking and the sense of community you gain. As an affiliate representative I want to help other early-career physiologists discover The Society.

Fiona Hatch is an Affiliate Representative and sits on the Education and Outreach Committee and the Policy Committee

For a full list of Council members, see www.physoc.org/council

Vacation Studentships

In 2013, The Society's Vacation Studentship scheme funded 39 students to gain hands-on research experience in the lab of a Society Member. We asked each of these students to prepare a report summarising their experience, achievements and results. The reports were then reviewed by Members of the Education and Outreach Committee and two were selected for publication in *Physiology News*.

Sam Bose

University of Bristol, UK

Having developed an interest in cardiovascular physiology and electrophysiology during my first two years as an undergraduate, I was keen to gain laboratory experience in these fields of research. After approaching Andrew James (Andy) from the School of Physiology & Pharmacology at the University of Bristol and deciding upon a project, I applied to The Society for a Vacation Studentship to work in Andy's lab over the summer. These studentships are designed to enable undergraduate students to undertake a research project lasting up to eight weeks during the summer vacation and cover living expenses for that period.

Our project aimed to investigate the potential for the anti-anginal agent, ranolazine, to be protective against atrial fibrillation. Atrial fibrillation is the most common arrhythmia and a major risk factor for stroke. Previous studies had highlighted an atrial-specific action of ranolazine, a property that would be beneficial due to the reduced risk of ventricular side effects. Ranolazine is a sodium channel blocker that inhibits a sustained component of the sodium current. Our aim was to investigate how ranolazine affects atrial electrophysiology and the inducibility of atrial tachyarrhythmia (AT) during metabolic stress in Langendorff-perfused rat hearts.

The first couple of weeks of the project consisted mainly of training, both in the use of the laboratory equipment and the interpretation of electrophysiological recordings. Although the University of Bristol provides a high degree of practical training to undergraduates, the work I was doing for this project went far beyond anything I had experienced before. Hearts were excised from adult male rats, mounted on a modified Langendorff-perfusion apparatus and electrograms recorded from the surface of the left atrium using a 5x5 electrode array. Being a big fan of all things bespoke, I enjoyed the fact that this array consisted of platinum/iridium wires embedded in dental resin using an eppendorf tube as a mould! As a self-confessed geek, I don't mind mentioning that the DIY nature of such equipment makes electrophysiology particularly appealing to me!

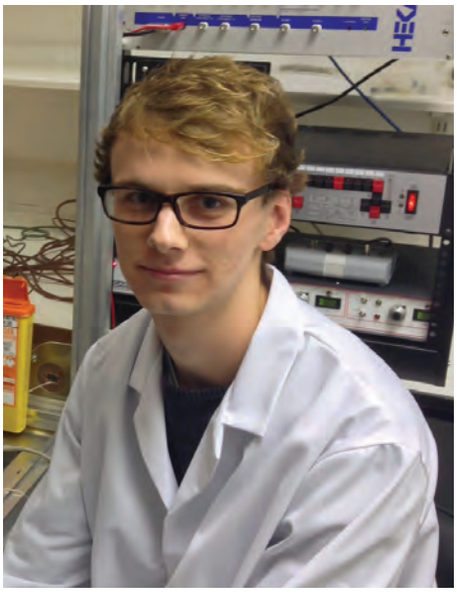
Having come to terms with the daunting setup of amplifiers, tubes and wires that I would be working with for the next eight weeks, the next task was to learn how to interpret the recordings. It took me many long hours of fiddling with wires and earth connections, and stimulating the heart at various current amplitudes before I was happy that I was able to distinguish actual electrograms from noise, baseline wander and stimulus artefact. However, once I knew what I was looking at and had confidence in my ability to interpret the traces, the experiments started to run smoothly and I was able to gather useful data.

The recording of electrograms enabled the measurement of both atrial effective refractory period and conduction velocity. The product of refractory period and conduction velocity provides the wavelength of excitation, increases in which are thought to provide protection against re-entrant arrhythmias. Our hypothesis was that although ranolazine would most likely cause a decrease in conduction velocity due to sodium channel block, the drug may also increase refractory period sufficiently to result in an overall increase in wavelength. In addition, we examined the effect of ranolazine on the inducibility of tachyarrhythmia during beta-adrenergically induced metabolic stress. Bursts of very rapid (>100 Hz) pacing were used to induce paroxysms of AT. Metabolic stress was produced by perfusion with the beta-adrenoreceptor agonist, isoprenaline.

Firstly, perfusion with isoprenaline markedly increased the inducibility of AT through reduction in the refractory period and wavelength. Ranolazine suppressed the development of AT during metabolic stress. However, this anti-arrhythmic effect was not correlated with changes in the wavelength of excitation. Although ranolazine prolonged the atrial effective refractory period and slowed conduction velocity, the drug did not completely prevent the metabolic stress-induced changes in these parameters. The study has opened the door to further research into the mechanism of suppression that was observed.

Being able to undertake this research project has confirmed my desire to pursue a career in research and has allowed me to experience firsthand what laboratory work involves. When the placement first started, I must confess to feeling a little out of my depth. I was scared of making silly mistakes or getting in the way of others. However I soon found myself gaining confidence and by the end of the project I felt at home in the lab. The work was challenging, but hugely satisfying when the results started to come through. My desire to pursue a PhD after graduating next summer is confirmed.

I would like to acknowledge the help and support of Andy James, Richard Bond, Jules Hancox and everyone from the University of Bristol Cardiovascular Research Laboratory with this project, as well as The Physiological Society for providing the funding that made it possible.



Jonathan Raby

University of Cambridge, UK

Over the summer of 2013 I spent eight weeks working on the molecular basis of acid pain sensation with Ewan Smith in the Department of Pharmacology, University of Cambridge. I am currently in my third year of an undergraduate medicine degree and wanted to gain some experience of the type of work and lifestyle associated with entering a research environment in order to decide whether pursuing a PhD and a career in research is right for me.

Before undertaking the project, my only previous experience of laboratory work was through practical sessions associated with my undergraduate degree, which have tended to be time-pressured and prescriptive. The studentship has given me a more realistic impression of what practical science is like, and I believe I have developed a better understanding of the patience and pragmatism required when undertaking research. In contrast to undergraduate practicals designed to be robust and predictable in outcome, sometimes the experiments and procedures I performed simply did not work (occasionally for no clear reason), and I was given some insight into the continuous process of troubleshooting and refinement that seems important for improving the chances of later success and the quality of data generated. I also experienced for the first time some of the excitement that stems from a novel, unexpected result and the challenge associated with formulating ideas and hypotheses that might explain the phenomena observed (by contrast, in undergraduate study the aim of experiments was generally to generate results consistent with established theory, and 'deviant' data were usually disregarded rather than explored).

My pre-conception of working in a lab held that it was a rather lonely existence, and that engaging in independent research could lead to a degree of isolation. However, my experience over the course of the studentship has shown me that a career in science can have far more of a 'team feel' than I had been expecting, and that there is great capacity for (and benefit in) collaborations within the lab, University or even internationally. The other members of the lab and department were extremely welcoming and generous with their time, and I enjoyed having the chance to get to know a particular department in the University as a research environment, and to interact with its members in a more personal, less one-directional way than had been possible during my undergraduate course.

The aim of my project was to explore the structural bases of the functional differences between the two acid sensing ion channels (ASICs) produced by alternative splicing of the ASIC1 gene (ASIC1a and ASIC1b). Responses of ASIC1a and ASIC1b to low pH stimulation differ both quantitatively and qualitatively, and the splice variants differ in their first 172αα, which suggests that domains within this region (including the intracellular N-terminus of the protein) confer the different properties observed. To improve understanding of the link between structure and function of ASIC1 splice variants, I created a novel chimera of naked mole rat ASIC1a and ASIC1b in which part of the N-terminus region of nmrASIC1b was replaced with equivalent amino acids from nmrASIC1a (this was achieved by a polymerase chain reaction using primers that amplified only the regions of each splice variant that were to form the chimera). I was trained in a range of microbiological techniques that allowed me to transfect Chinese hamster ovary cells with plasmid vectors carrying either nmrASIC1b or the 'AB1' chimera. I then investigated the biophysical properties of each channel type using the whole-cell patch-clamp technique. The responses of the transfected cells to different low pH solutions were measured using various experimental protocols designed to characterise channel properties including response magnitude, inactivation time constant, current-voltage and dose-response relationships. In summary, the 'AB1' chimera behaved much more similarly to nmrASIC1a than to nmrASIC1b, suggesting that the N-terminus plays a critical role in channel function (Fig. 1 shows that the AB1 inactivation time constant is significantly different to that of nmrASIC1b and highly similar to that of nmrASIC1a).

The Physiological Society Vacation Studentship allowed me to undertake a research project that has been influential in shaping my career plans and scientific interests. Given the stimulation and satisfaction that I found in even a short period of time spent in the lab, I am now certain that I would find a career in science exciting and fulfilling. I am currently exploring the various routes by which I could pursue a PhD while continuing to progress in my medical career. The project I worked on has confirmed an interest in the physiology of pain sensation, which has meshed with a pre-existing clinical interest in anaesthesia. However, undertaking the project has also given me a better appreciation of the huge range of exciting research opportunities that exist within the physiological sciences, and so I intend to keep an open mind as to the exact nature of any PhD I may undertake for as long as possible.

I acknowledge the supervision of Laura-Nadine Schuhmacher and Ewan Smith.

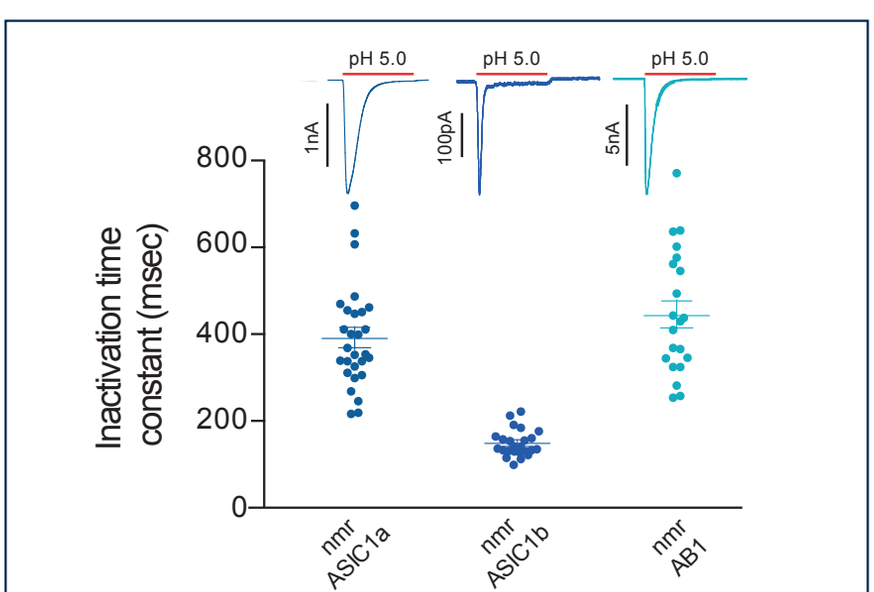
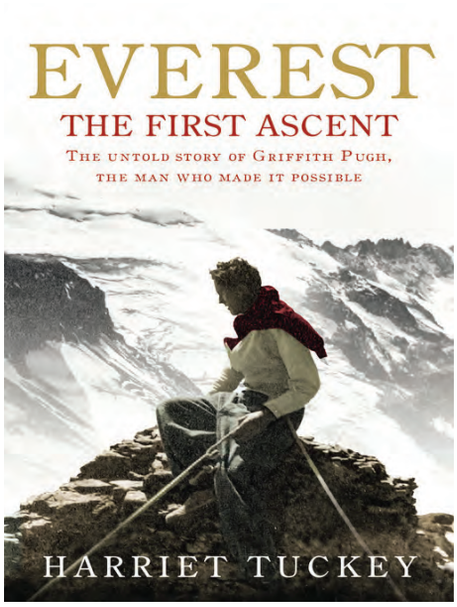


Figure 1. Inactivation time constants for nmrASIC1a, nmrASIC1b and nmrAB1 following a 5 second stimulation with a pH 5.0 solution

Book review: Everest: The First Ascent By Harriet Tuckey

Austin Elliot

University of Manchester



Ebury Publishing

ISBN: 978-1846043482

Griff Pugh and the young Harriet Tuckey, taken at Heathrow airport on the 1953 Everest expedition members' return to the UK.

It is a cliché when a review tells you 'read this book' – but sometimes it is justified. Harriet Tuckey has produced, in nearly a decade's labour, a marvellous biography of her father, Griff Pugh, a pioneer of post-war human applied physiology. If you are interested in scientific biography, or the history of – inter alia – mountaineering, high-altitude physiology, exercise physiology, studies of hypoxia or human thermoregulation, this book is for you. Anyone teaching students in any of the above areas will find it a brilliant source of anecdotes and history, as well as a pleasure to read.

Griff Pugh (1909–1994) was the key scientific consultant to, and a member of, the 1953 British Everest expedition that made the first successful summit attempt on the world's highest mountain. As Tuckey recounts, his input encompassed designing the expedition's boots, clothing, tents and stoves, in addition to determining the oxygen-breathing regimes, fluid intake schedules – critically important, and neglected in all previous expeditions – food and personal hygiene recommendations and diets and supplies. The success of the 1953 Expedition, where several celebrated British expeditions of the '20s and '30s had failed – most famously the 1924 one where the climbers George Mallory and Sandy Irvine disappeared – was quite likely down to the systematic scientific approach adopted. Indeed, Pugh's ideas became the blue-print for high-altitude climbing with oxygen over the following two decades and beyond.

Though Pugh's key role in the Everest ascent has been reasonably well-known in the scientific and medical community via the writings of co-workers like (1953 Expedition doctor) Mike Ward, Jim Milledge and John West, it is largely missing from the popular accounts of the Everest ascent that appeared at the time and afterwards. Tuckey makes the case convincingly that this reflected in large part the desire of key figures like expedition leader Sir John Hunt to present the ascent as a triumph of the 'heroic human spirit' – and more specifically of the Imperial British one. This, together with a kind of instinctive distaste for science that Tuckey traces to the pre-war public school amateur ethos prevalent in the climbing clubs, means that Pugh's role in the expedition has remained grossly under-appreciated. Pugh himself – characteristically – also contributed to his being edited out of the record by never writing a definitive mass-market account of his work.

Pugh, an Olympic skier and doctor who came to physiology via wartime work running a mountain warfare ski school in the Lebanon, spent his entire scientific career working for the MRC. Though highly regarded by his scientific peers, and notably by Institute Director Sir Peter Medawar, Pugh never attained great organisational rank or prominence – largely through his disdain for administration and office politics. His eccentricity in his chosen 'irascible gentleman scientist' persona comes over strongly in Tuckey's book. The most striking anecdote is the one where Pugh, driving his pregnant and in labour wife, Josephine, to hospital in his beloved sports car, drops in at an Everest Expedition Reunion Party at the Café Royal in Regent Street for a few minutes and then forgets he has left her waiting outside in the car.

Though Pugh's high-altitude work on the Everest ascent and the later 1960 Silver Hut expedition gets pride of place, Tuckey also gives fascinating accounts of his work with endurance swimmers and elite athletes, and his interest in outdoor survival. She rightly emphasises the real-world consequences of her father's work. Pugh's influence was truly far-reaching, even if his name has been largely forgotten outside science.

The book is also a touching account of really getting to know a parent posthumously. Tuckey and her father were estranged during his life, and the book movingly describes her journey, long after his death, to an appreciation of him and his work. As she writes, it is through this investigation that she manages to understand her father in a way which had eluded them during his life. This personal voyage, deftly described, runs through the book like an additional thread,

In summary, this is a wonderful book. You should read it.

Would you like to submit a book review to *Physiology News*? Please get in touch with us on **magazine@physoc.org**

Marianne Fillenz

1924 – 2013

Marianne Fillenz

All Members of The Physiological Society will be sad to hear of the death of Marianne Fillenz at the age of 88 from cancer. Those of us in Oxford will miss her especially. After 60 years here she seemed to be a permanent fixture. We will miss her exceptional friendliness, her interest in everything from local gossip to the place of humanity in the universe, her positive outlook and her quizzical responses to incautious remarks. Generations of colleagues and students have cause to be grateful for her great patience and deeply conscientious attention to making sure that she understood their problems and that they understood what she was trying to tell them.

Marianne was born in 1924 in Timisoara, Romania. Her mother was Viennese and her father a Hungarian Jew. Correctly predicting the march of Nazism into Romania, in 1939 they left for New Zealand. The choice of New Zealand was completely accidental; Jewish friends had a spare form for New Zealand and passed it on to them. However what a fortunate accident! In New Zealand she met two of the most important influences in her life, the philosopher, Karl Popper, and the new Professor of Physiology at Otago, Jack Eccles, who had just arrived in New Zealand from working with Charles Sherrington in Oxford. Both were inspirational to her, and Marianne maintained their friendships, her deep interest in philosophy and in physiology, throughout her life.

Jack Eccles inspired her life choice of research physiology during her preclinical medical studies at the University of Otago and she never looked back. Her first paper was published in 1946 in the *Journal of Neurophysiology*; it was on the acetylcholine endplate potential in skeletal muscle. Such was her talent that Eccles persuaded her to interrupt or abandon her medical studies to undertake a DPhil in Physiology at Oxford. She remained intensely loyal to Jack. I remember that she was very helpful to me in the 1970s: as a newcomer to Magdalen College it was my duty to entertain Eccles when he came back to his old College after his retirement in Switzerland, and knowing him so well, she was able to reminisce about old times with him, which relieved me greatly. It is fitting that her last paper published in 2012 was on his life and work.

She arrived at Somerville College in 1950 and she remained in Oxford for the rest of her life. She did her DPhil with Sybil Cooper and David Whitteridge, studying receptors responding to stretch of the eye muscles. Her paper on this, published with Sybil in *The Journal of Physiology* in 1955, is a classic. How we know where our eyes are pointing is still contentious and the question of what sensory endings supply the brain with information about eye muscle length is still unsettled to this day, since typical muscle spindles are not found in these muscles. But Marianne's work showed clearly that an eye muscle length signal is indeed supplied to the brain in the cat, and this was much later confirmed in humans.

This work taught Marianne how to record from single nerve fibres in peripheral nerves and from single nerve cells in the brain stem. I can attest to her skill because some years later she managed to teach numbskull me to record from single fibres in the vagus nerve. By this time she had moved her main interests from eye muscles and vision to her subsequent lifelong study of the autonomic nervous system and its control, and for the next 30 years she became the local expert on the anatomy and physiology of the autonomic nervous system.

Marianne was not content simply to use techniques she had already learnt; she eagerly sought out new methods that she thought might help her to understand the control of the autonomic nervous system better. So she was one of the first people to use and develop the technique of voltammetry to measure catecholamine release deep in the brain. Her paper on linear sweep voltammetry to measure dopamine release in the rat striatum is another classic, and her technique is still much in use today. With John Albery she went on to develop voltammetry electrodes for conveniently measuring many other substances, such as glucose, alcohol, amino acids, oxygen, CO_2 and N_2O.

As well as a highly productive research scientist, Marianne was a devoted and much loved teacher. After her DPhil she spent nine years as a college lecturer at St Hilda's and as a University 'Demonstrator' in the Department of Physiology, and in 1963 she won a Tutorial Fellowship at St Anne's College. She was a loyal member of St Anne's for the rest of her life. With her wide interests spanning philosophy, social policy, politics and the arts (she was an excellent pianist, and regular concert goer) she was an extremely popular member of the SCR. Teaching mainly female undergraduate and graduate medical and physiology students, she was particularly keen to encourage her women students not to feel that family commitments would inevitably reduce their scientific productivity and she revelled in their successes when they came. She was a tenacious rationalist, so that both students and colleagues had to be on their toes. Her favourite phrase was, 'Really, you believe that!' after which you knew you were in for some hard defending. Her helpfulness, humanity and breadth of interests captivated her pupils and colleagues alike.

All this time not only was she very productive scientifically and teaching full-time, but also she brought up three children highly successfully and with the minimum of outside help. This was assisted greatly by the unusual amount of support given to her by her husband, John Clarke, who sadly predeceased her by two years. He was a strikingly tall and handsome Rhodes Scholar from Western Australia, studying hypothalamic control of the reproductive system, which he continued throughout his, also highly productive, life. They met during their first term at Oxford and they were married a year later. John was an amazingly 'modern' father who put the rest of us to shame; for instance he would seldom go to lunch in College as most donnish fathers did, but insisted on returning home to help Marianne give their children their lunch – he was meticulous in shouldering his half of all their child care responsibilities.

Marianne was also a keen Member of The Physiological Society and most of her early publications were originally in the form of The Physiological Society Proceedings. Many Members will remember her unfailing reasonableness and courtesy when she was chairing the often heated discussions following a presentation. We will all miss her greatly.

John Stein

Maureen Young

1915 – 2013

Maureen Young

Maureen Young was born on 16 October 1915 in Southwold, Suffolk, England. Her mother, Ina Heslop, was Irish and her father, William Young, was English. They met in Dover where Ina was nursing the sick and wounded of World War I and William was a doctor waiting to embark for service in France. Her early childhood was spent with her younger brother in London where her father was a pathologist at Guy's Hospital after the war. When she was ten, her parents moved to a posting in Singapore and she was sent to boarding school, Northwood Girls School, where practical lessons in chemistry and biology awakened her interest in science. Her father was keen that girls should be educated and financially secure so he was happy to pay the fees for Maureen to attend Bedford College for women when she finished at school.

Maureen was a student at Bedford College from 1932 to 1938, a long period as an undergraduate by today's standards. First, she had to take an intermediate year in chemistry, physics, botany and zoology as she had not taken higher qualification examinations at school. When she failed physics at the end of the first year, she had to repeat the year. She then proceeded to a three-year general degree in physiology, chemistry and zoology followed by a one-year special degree in physiology, graduating with 2nd class BSc (Special) in 1938. For the summer vacations of both 1937 and 1938, Maureen went to Germany to learn German, an essential language for scientists then, and saw firsthand the Nazi preparations for war. In the early years of WWII, Maureen worked with the Blood Transfusion Service, based partly in at St Thomas' Hospital, helping to develop an acid-citrate glucose solution for the storage of whole blood. These studies led to her first publication in 1940. By 1942 she was back at Bedford College as a demonstrator in physiology, although the College had been evacuated to Cambridge by then. From 1942 to 1945, she therefore worked in the Physiological Laboratory in Cambridge, teaching Bedford College students and carrying out research with Professor Joseph Barcroft. He had been Head of Department of Physiology but by 1942 was in his 70s with failing eyesight. He recruited Maureen to take blood samples from the tiny carotid arteries of fetal rabbits to measure developmental changes in the oxygen content of fetal blood. This initiated Maureen's life-long interest in fetal physiology.

After the war, Maureen moved to St Thomas' Hospital as a demonstrator in physiology when the medical schools started to appoint women to the teaching staff with the new compulsory intake of 15% women students. However, despite her previous research experience, it was not considered suitable for her to teach medical students reproductive physiology for several years after her appointment! Over her career at St Thomas', she taught many aspects of physiology to Second MB medical students and ran an intercalated BSc course, first in the Physiology Department and, then, in the University Department of Obstetrics and Gynaecology (O&G) where she had transferred as a senior lecturer on its formation in 1964. For 18 years, she ran a research unit in O&G at St Thomas', becoming Professor of Perinatal Physiology before her retirement to a village near Cambridge in 1982. During her career, she had several periods working abroad, at Yale, UCLA, North Western University Chicago and in the Department of Obstetrics in Perth, Australia, which established life-long international collaborations and friendships.

Even after retirement, she continued with research and academic work as a visitor at the Babraham Institute and an associate editor of *Placenta*.

At St Thomas', her initial research focused on the placental transfer of curare and other drugs using rabbits and guinea pigs and then on the adaptations to the newborn circulation in collaboration with clinical colleagues. Finally, her interests moved onto fetal growth and nutrition with particular emphasis on placental transfer of amino acids and the role of insulin in fetal protein turnover in a wide range of species including guinea-pigs, rabbits, sheep and horses. She published well over 100 peer-reviewed original papers, many in *The Journal of Physiology*, as well as reviews and chapters in books, in a publishing career that spanned 63 years from 1940 until she was 88 in 2003. She was an enthusiastic member of several physiological and paediatric societies, being elected to The Physiological Society in 1944. She was a founder member of the Neonatal Society and its President from 1984 to 1987. She regularly attended national and international meetings well into her 80s.

Maureen was a pioneer in many ways. She was one of the first women to secure a teaching position in a medical school. She championed the professional recognition of women in an era when female academics were rare. She was an active advocate of fetal physiology and the need for basic research to underpin advances in medicine. She was a role model for active retirement, enjoying the freedom from teaching and administrative work to continue pursuing scientific questions through her extensive network of collaborators and colleagues. She was also an inveterate traveller, visiting places like Iran, Hong Kong, Russia and Latin America, often alone, long before travel to these places was easy or entirely safe for Western Europeans. She will be remembered for her many kindnesses to younger academics and clinicians and for her infectious enthusiasm for placental and fetal physiology.

Abigail Fowden

The Society also regrets to announce the death of:

Alan Howe, former Halliburton Professor of Physiology at King's College London

Notices and full obituaries can be found The Society website at www.physoc.org/obituary-notices

The Journal of Physiology

Special Issues

The Journal of Physiology is pleased to announce that it has a pipeline of high-quality special issues lined up for 2014. Readers can expect to see collections of papers covering renal physiology, glutamate receptors, neurohormonal signalling in the gastrointestinal tract and papers on the integration of evolutionary biology with physiological science.

New Consulting Editor

We are delighted to welcome to the Editorial Board Bengt Saltin as a new Consulting Editor. Prof. Saltin has a long publishing and reviewing history with *The Journal* and complements the existing group of Consulting Editors. Prof Saltin is a world leader in the field of muscle and exercise physiology and acts to strengthen our interest in this important area of research.

Join the debate

We have recently published our tenth CrossTalk debate on whether or not the diaphragm muscle atrophies as a result of inactivity. Due to the success of the debates so far, we would be interested to hear whether you have any ideas for future debate topics. If you'd like to send a suggestion, please contact **journals@physoc.org**

Review of peer review process & system

The review of *JP*'s and *EP*'s peer review processes and manuscript management system is underway and we are making good progress.

We would welcome your input, so please send your comments and suggestions to Alexandria Lipka at alipka@physoc.org

Launching free iPad apps for *The Journal of Physiology* and *Experimental Physiology*

You can now enjoy an optimized browsing and reading experience, where you can download issues, stay up to date with the latest articles published and save/share your favourites. You can find more information at **www.physoc.org/journal-app-instructions**

Experimental Physiology

Virtual issue for SfN and AHA

Experimental Physiology created virtual issues for promotion at the SfN and the AHA meetings in November. The issues highlight selected articles that have recently been published in the Autonomic Neuroscience and Cardiac Muscle sections of *Experimental Physiology* that are likely to be of interest to those attending the 2013 SfN and AHA meetings, respectively. Articles are freely accessible online until the end of 2013.

'The Physiology and Pathophysiology of Obesity' - call for papers

In September 2014 *Experimental Physiology* will publish a themed issue in conjunction with the Society's 2014 Topic Meeting called 'The Physiology and Pathophysiology of Obesity', containing review articles and keynote lectures on this important topic. The issue will also welcome high quality original, peer-reviewed articles from active researchers in this field. Publication of the issue will be scheduled to coincide with The Physiology of Obesity topic meeting providing contributing authors with an excellent opportunity to show case new findings to their target audience in a highly focused and consolidated issue. Please see **www.physoc.org/obesity2014** for more information.Submit online by 1 April 2014 at **http://submit.expphysiol**. Articles accepted for publication in the issue will be published individually on acceptance before being published within the themed issue. For further information or to submit an article see the *Experimental Physiology* homepage at **http://ep.physoc.org**

Physiological Reports

Celebrating success

Physiological Reports has got off to a very good start. The American launch took place at Experimental Biology 2013 in Boston on 21 April, the first research article was published on 7 May, the European launch took place at IUPS 2013 in Birmingham on 22 July, and the hundredth research paper was published on 16 October. In addition to the usual four Editor's Choice articles when each issue is closed, the Editor-in-Chief has selected three to celebrate the first hundred (all the Choice articles this year for all three of The Society's journals can be found at **http://bit.ly/119DOXY**)

Physiol Rep, its official truncated name, uses the continuous publication model, in which articles are published as soon as possible after the authors' corrections have been made. The articles are not presented as one ever-lengthening list, as at some new journals, but are instead assigned to an open issue, and each issue is closed at the end of the month and a new one opened. The journal thus has volumes and issues the traditional way, and all that is missing is page numbers.

What's coming up in the future? At present *Physiol Rep* is published only at Wiley Online Library, but a second publication site at HighWire is being readied, using the new interface already in use by the American Physiological Society's journals. iPad apps are being prepared for both sites. By the end of the year *Physiol Rep* is expected to be thoroughly established among the physiological community's journals.

The Big Bang
UK Young Scientists & Engineers Fair

Big Bang Fair in Birmingham: Call for Volunteers

We are pleased to announce that The Physiological Society will be joining the celebration of science, technology, engineering and maths at the next Big Bang Fair. The national event takes place in March every year and aims to show young people the many exciting and rewarding opportunities available in STEM subjects. This next fair is in Birmingham, and will be running from 13–16 March. Our stand will be based on our 2014 theme Understanding Obesity, and we are looking for volunteers in the local area who can help run our activities. Please contact **outreach@physoc.org**

Trustees and staff of The Physiological Society wish all Members a very merry festive season and a successful New Year.

We look forward to your support in our 2014 activities and to seeing you at our events.

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